Memory of chirality in rebound cyclizations of α-amide radicals

Aniruddha Sasmal, Tsuyoshi Taniguchi, Peter Wipf, and Dennis P. Curran

Abstract: Reduction of (*S*)-*N*-(2-bromoallyl)-*N*-(*tert*-butyl)-2-methyl-3-phenylpropanamide with tributyltin hydride provides (3*S*,4*S*)-3-benzyl-1-(*tert*-butyl)-3,4-dimethylpyrrolidin-2-one with about 80% retention of chirality at the stereocenter adjacent to the amide carbonyl group. This memory of chirality is suggested to occur by transfer of chirality from a stereocenter to an axis, then from the axis back to a new stereocenter.

Key words: memory of chirality, radical reactions, amides, stereochemistry.

Résumé : La réduction du (*S*)-*N*-(2-bromoallyl)-*N*-(*tert*-butyl)-2-méthyl-3-phénylpropanamide par l'hydrure de tributylétain conduit à la formation de la (3*S*,4*S*)-3-benzyl-1-(*tert*-butyl)-3,4-diméthylpyrrolidin-2-one avec 80 % de rétention de la chiralité au stéréocentre adjacent du groupe carbonyle de l'amide. Il est suggéré que ce souvenir de la chiralité résulte d'un transfert de chiralité du stéréocentre vers un axe, puis de cet axe vers un nouveau stéréocentre.

Mots-clés : souvenir de la chiralité, réactions radicalaires, amides, stéréochimie.

[Traduit par la Rédaction]

Radical reactions involve open-shell intermediates and therefore tend to occur much more rapidly than ionic and pericylic reactions involving closed-shell species.[1] Indeed, many radical reactions can occur on timescales comparable to or faster than common conformational changes of organic molecules, including simple bond rotations. This speed makes radicals attractive for reactions that involve transient conformational chirality.

Depending on the overall transformation, reactions with transiently chiral intermediates can exhibit transfer of chirality or memory of chirality (MOC).[2] An example of each reaction type is shown in Fig. 1. Cyclizations of *o*-haloanilides are typified by the reductive cyclization of **1** to give **3** via the intermediacy of axially chiral radical **2**.[3] Levels of transfer of axial chirality from **1** to the new stereocenter in **3** are high even when the ortho substituent R is hydrogen.[3b] Simple rotation of the anilide N–Ar bond is a racemization reaction that would erase the chirality transfer, so clearly cyclization of **2** is faster than this rotation.

Memory of chirality occurs at a stereocenter when a formal substitution reaction proceeds stereoselectively even though the reaction passes through a trigonal intermediate.[2a] Rychnovsky and co-workers[4] have shown that radical reactions can be faster than ring interconversions, while Giese and co-workers[5] and Bertrand and co-workers[6] have shown that onward reactions of diradicals (for example, coupling) can compete effectively with simple σ-bond rotations. Bonjoch and co-workers[7] discovered intriguing examples of MOC in monoradical reactions that involved hydrogen transfer and cyclization of α-aminyl radicals.

In an example from Bertrand and co-workers,[6b] heating of **4** provides **6** with a high degree of retention of configuration at the stereocenter bearing the carbomethoxy (CO_2Me) group. This reaction must involve an axially chiral intermediate like **5** that is generated by enediyne cyclization and 1,6-hydrogen atom transfer. Onward reaction of α-aminyl radical **5** to form the product must be faster than CH_2–N bond rotation. In other words, the MOC results from a back-to-back relay of chirality transfer reactions: from a stereocenter to an axis, then from the axis back to a new stereocenter.

We wondered whether the electron-donating nitrogen substituent is indispensible in such types of MOC reactions. Indeed, there is some old circumstantial evidence that it is not. In 1968, Heiba and Dessau[8] reported that the atom transfer addition of chloroform to enantioenriched **7** gave a lactone product (**8**) with a small residual optical rotation. The enantiomeric excesses (ees) were not known for either **7** or **8**, so the significance of the residual rotation is unclear.

This transformation presumably involves addition of $Cl_3C\bullet$ to **7** followed by ester C–O bond rotation to give **9** and radical translocation[9] by 1,5-hydrogen atom transfer to give **10**. MOC will occur if the 5-exo cyclization of **10** is faster than rotation of the σ bonds to the carbonyl carbon and net retention is expected. This sequence of translocation and rebound cyclization is reminiscent of both Bertrand and co-workers'[6] and Bonjoch and co-workers'[7] MOC processes.

Received 14 June 2012. Accepted 13 September 2012. Published at www.nrcresearchpress.com/cjc on 29 November 2012.

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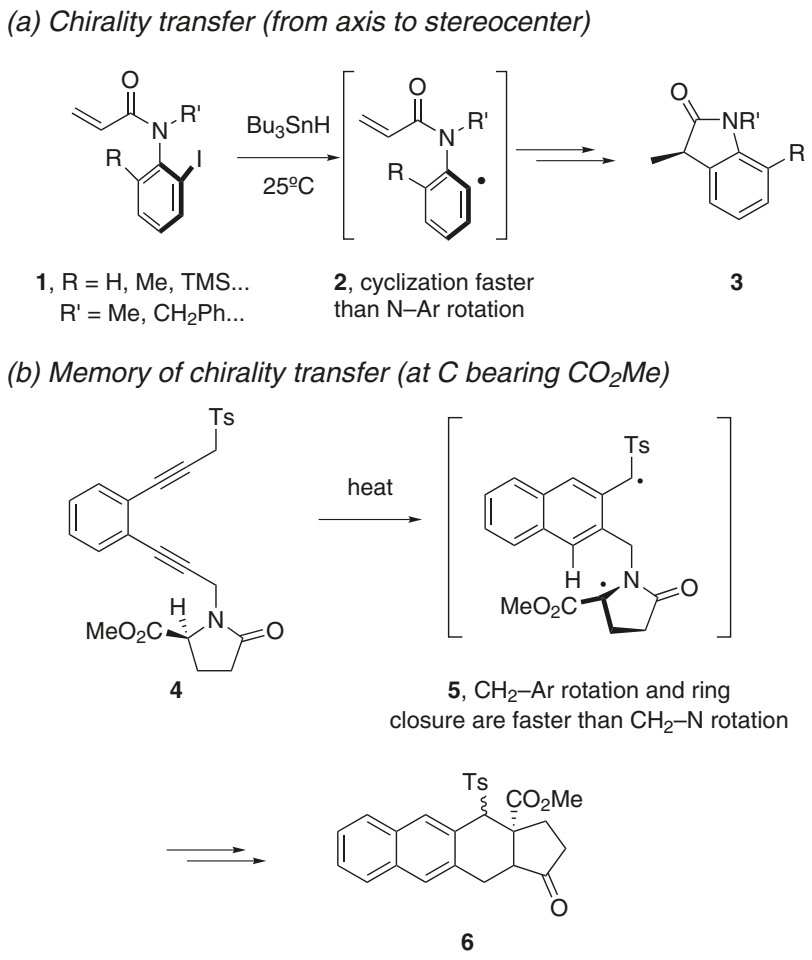
This article is part of a Special Issue dedicated to Professor Derrick Clive in recognition of his contributions to organic chemistry, especially radical reactions.

Fig. 1. Examples of radical intermediates in (*a*) transfer of chirality and (*b*) memory of chirality.



The memory effect can be spoiled by rotation of either the C–C bond to the carbonyl group of **10** (racemization results) or the C–O bond (an unfavorable geometry for cyclization results).

At the core of this postulate is the notion that ester-substituted radicals like **10** resemble α-substituted acrylates and related molecules.[10] Despite conjugation, their ground-state geometries are twisted owing to unfavorable steric interactions in the otherwise favored planar forms.[11] This is important because the planar form of **10** is achiral. In short, the assumption that **8** must inevitably be racemic (because a trigonal intermediate is involved) is not on solid footing.

To start, we reproduced the cyclization of enantiopure **7** and confirmed that the small rotation of **8** is not an artifact.[12] But we could not easily determine the enantiomeric composition of **8**. It decomposed on GC injection, and the use of shift reagents was complicated because **8** is already a mixture of diastereomers (Supplementary data).

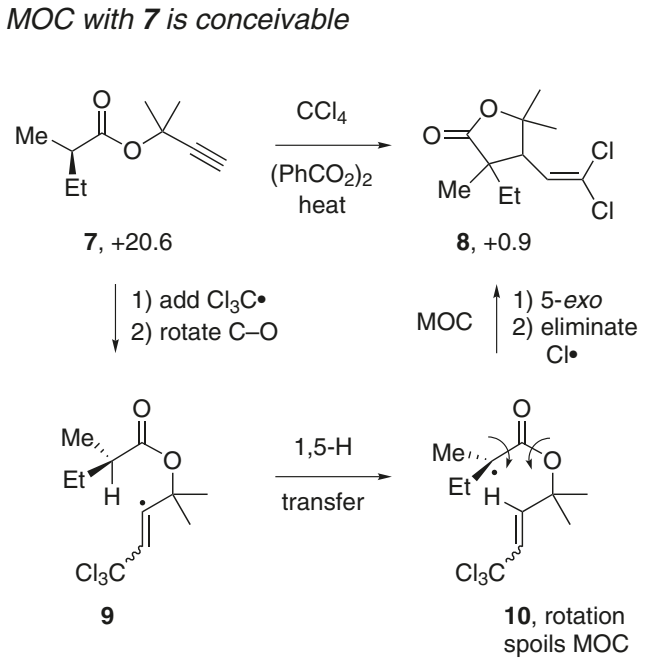
Instead of trying to solve the analytical problems with **8**, we retooled the precursor in three ways. First, we replaced the ester with an amide. One of the two amide substituents is always well-positioned for both 1,5-hydrogen transfer and subsequent cyclization. This eliminates the problem of the unfavorable rotation trans geometry at the ester C–O bond of **7**. Second, the addition reaction of $Cl_3C\bullet$ is not an essential component of the process, so we designed it out, leaving an alkenyl halide as a direct precursor of the alkenyl radical needed for 1,5-hydrogen abstraction. Third, we removed the geminal methyl groups of **7**. This gives precursors **11a**–**11c** shown in the lower part of Fig. 2.

The first substrate studied was amide **11a**, which exists as a roughly 1:1 mixture of *E*/*Z* amide rotamers[13] (structure **11a** shows the favorable rotamer for MOC chemistry). The study of this compound proved to be a wrong turn, though we prefer to regard it as a short scenic detour. Reduction of racemic **11a** with tributyltin hydride in refluxing toluene provided a crude product that did not apparently contain either the target MOC product or the directly reduced product. Instead, the major product was **12**, which was isolated in a 50% yield by flash chromatography.

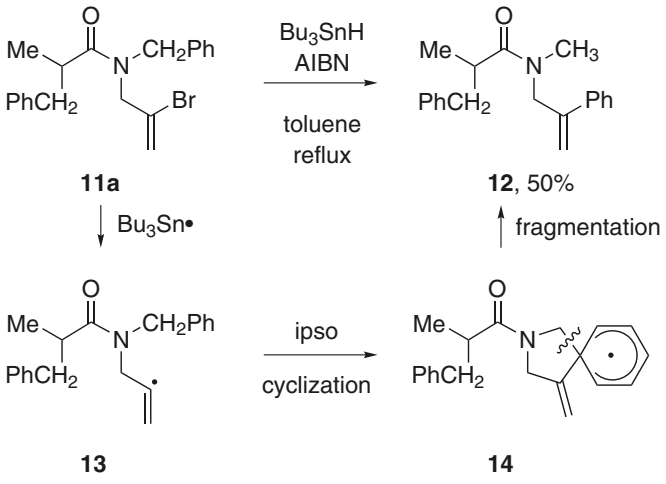
Compound **12** is a rearranged product of 1,4-phenyl transfer that presumably forms by ipso cyclization of **13** to give **14** followed by fragmentation, as shown in Scheme 1. The mechanism was supported by a reduction of **11a** with Bu_3SnD, which gave **12** with significant deuterium labeling on the $N–CH_3$ group. Related aryl transfer reactions are well-known,[14] although none apparently with this structural motif. With optimization, this reaction could be useful for preparing β-aryl allyl amides and related molecules.

To eliminate competing phenyl migration, we targeted precursors **11b** and **11c** bearing *N*-*tert*-butyl groups in place of the *N*-benzyl group of **11c**. Precursors **11b** and **11c** exist as one major rotamer in solution,[13b] which has the *tert*-butyl group

Fig. 2. Top: Could memory of chirality have occurred in this old reaction of an α-chiral ester? Bottom: A retooled amide **11** eliminates potential problems.



Scheme 1. An interesting phenyl transfer reaction provides a short scenic detour.



cis to the amide oxygen atom, as drawn in Scheme 2. These precursors were synthesized in racemic and enantiopure forms,[12] and the results of key reduction experiments are summarized in Scheme 2. Direct reductive debromination of these precursors was a consistent problem, and higher yields of the target cyclized products (**15**) were obtained at higher temperatures. We settled on standard conditions involving syringe pump addition of Bu_3SnH and 2,2′-azobisisobutyronitrile (AIBN) in toluene to a refluxing solution of the precursor in toluene. The target products were isolated by flash chromatography, then analyzed by spectroscopy and chiral GC.

The reduction of (*rac*)-**11b** in this way provided about a 1:1 mixture of diastereomers **15b** in a 39% isolated yield. We could not separate these diastereomers, nor could we make a clear cis/trans assignment. Nonetheless, the sample of (*rac*)-**15b** exhibited four peaks on chiral GC, showing that both pairs of enantiomers were resolved. Cyclization of (*S*)-**11b** (>99:1 enantiomeric ratio (er)) provided the same ratio of diastereomers **15b** in about the same isolated yield, but now both diastereomers were significantly enantioenriched to the extent of about 84:16.

While we learned the enantiomer ratios of **15b**, it was not easy to preparatively separate the diastereomers or to assign their configurations in the mixture. To simplify the assignment problem, we selected **11c** with the hypothesis that one diastereomeric radical resulting from cyclization would cyclize again, whereas the other would not.[15] Tin hydride reduction of (*rac*)-**11c** provided a mixture of products including the product of direct reductive debromination (about a 30% yield), a small amount of an isomeric cyclized product (<5%),[16] and the target products (*rac*)-**15c** and tricycle **16**. The products were partially resolved by chromatography; the reported yields (16% and 9%) are from pure fractions.

In contrast with **15b**, **15c** is a single diastereomer, which we assign as having the vicinal α-benzyl and β-methyl groups trans. The cis isomer was not detected in the crude product mixture. We believe that the cyclization of the translocated radical gives both isomers, one of which is reduced and the other of which cyclizes (see the following). This is why the yields of **15c** (trans only) are about half of the yields of **15b** (cis/trans mixture).

Reductions of (*S*)-**11c** and (*R*)-**11c** provided the products **15c** in similar yields to the racemate, but now significantly enantioenriched. The ratio of enantiomers (*S*)-**15c**/(*R*)-**15c** was 78:22 starting from (*S*)-**11c** and 21:79 starting from (*R*)-**11c**. These values of chirality transfer are comparable to those seen in the diastereomers of **15b**.

With a diastereopure sample now available, the assignment of absolute configuration was accomplished by experimental and computational rotation methods. The measured specific rotations of **15c** are +44.6 and −44.3 (*c* 0.25, $CHCl_3$). The specific rotation of (*S*,*S*)-**15c** was calculated by established techniques to be +125 in $CHCl_3$.[17] From the measured rotation of enantioenriched samples, the rotations of enantiopure samples of **15c** are about +77 and −77, respectively. While the values of measured and calculated rotations differ somewhat, it seems clear because of the large magnitudes involved that the dextrorotatory enantiomer has the (*S*,*S*) configuration. This means that the conversion of **11c** to **15c** (and by analogy **11b**

Scheme 2. Memory of chirality in reductions of **11b** and **11c**.

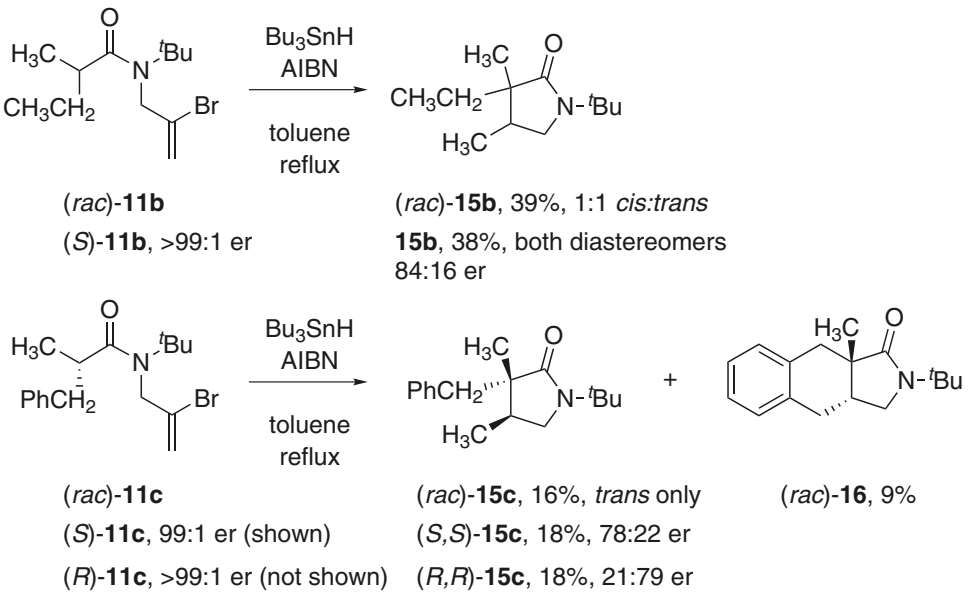
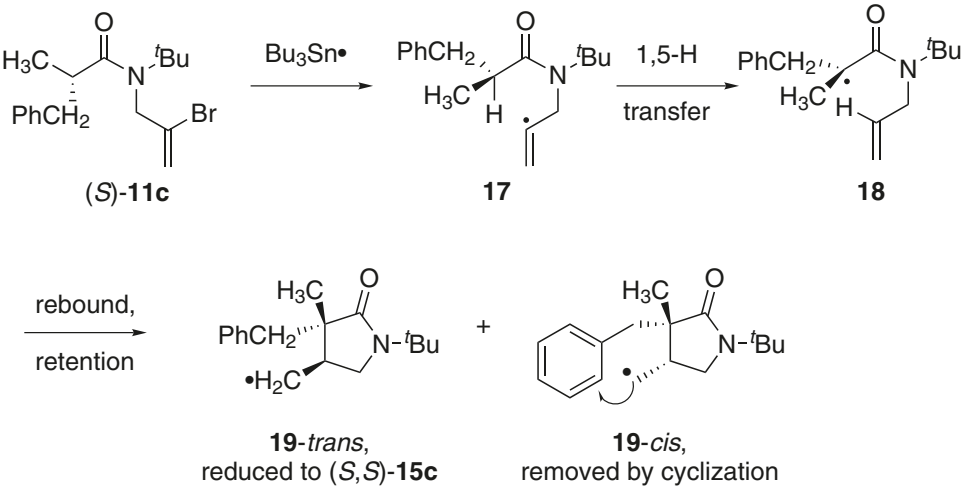


Fig. 3. Proposed pathways in the reduction of **11c**.



to **15b**) occurs predominately (about 80%) with the retention of configuration.

Figure 3 shows suggested pathways for the reduction of (*S*)-**11c**. Bromine abstraction provides alkenyl radical **17**, which in turn abstracts a hydrogen atom adjacent to the carbonyl group. Because of geometric requirements, the abstracted hydrogen is not aligned with the carbonyl π orbitals but is instead positioned roughly anti to the carbonyl group. This reaction erases the stereocenter but provides axially chiral radical **18**. Rebound cyclization of **18** to the alkene completes the MOC process, which must occur with retention. Now the diasteromeric products **19**-*trans* and **19**-*cis* take different pathways with **19**-*trans* being reduced as usual. However, **19**-*cis* is derailed by cyclization to the aryl ring, thereby simplifying the product analysis.

In summary, *N*-(2-bromo-2-propenyl)-*N*′-*tert*-butyl amides bearing a tertiary stereocenter adjacent to the amide carbonyl group undergo a sequence of radical reactions whose key steps are radical translocation (by 1,5-hydrogen transfer) and rebound 5-exo cyclization of the resulting α-amidyl radical to the resulting alkene. Even though a trigonal radical intermediate is formed, the γ-lactam product is produced with about 80% retention of configuration. This MOC is suggested to occur by transfer of chirality from a stereocenter to an axis, then from the axis back to a new stereocenter. The work suggests that generation of α-amide and related α-carbonyl (α-ester, α-keto, and so on) radicals by radical translocation might be a general route to reactions involving MOC of preformed tert-α-stereocenters in such precursors.

Supplementary data

Supplementary data are available with the article through the journal Web site http://nrcresearchpress.com/doi/suppl/10.1139/v2012-085.

Acknowledgements

We thank the National Institutes of Health for funding of this work.

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New and improved methods for the conversion of nitroalkanes into geminal chloronitroso compounds

Rafael Bou-Moreno, Sandra Luengo-Arratta, Valérie Pons, and William B. Motherwell

Abstract: The scope and limitations of a new method for the preparation of geminal chloronitroso compounds involving treatment of a nitronate anion with oxalyl chloride are described in full, and a milder, high yielding, and more chemoselective variant using the derived silyl nitronate is presented.

Key words: geminal chloronitroso, silyl nitronate.

Résumé : On présente une description complète de la portée et des limitations d'une nouvelle méthode de préparation de composés chloronitroso géminés impliquant le traitement d'un anion nitronate par du chlorure d'oxalyle et d'une légère variante, plus chimiosélective et conduisant à des rendements légèrement supérieurs, qui fait appel à l'utilisation d'un dérivé nitronate de silyle.

Mots-clés : composés chloronitroso géminés, nitronate de silyle.

[Traduit par la Rédaction]

Introduction

In recent years, the wide-ranging reactivity of the monomeric nitroso group[1,2] has served as a cornerstone for a variety of very useful reactions. As a colourful chameleon, it has been used inter alia, as a radical trap,[3] an ambident electrophile for both amination[4] and oxyamination[5] in aldol-like reactions, and perhaps most prominently, as a partner in the hetero-Diels–Alder reaction. The subset of geminally functionalized α-chloronitroso compounds, as with their α-acetoxy congeners,[6] has proven to be especially useful, since a subsequent hydrolytic cleavage leads to liberation of a free amino group. Reactions such as electrophilic amination using the Oppolzer sultam,[7] the beautiful chiral variant of the heteroene reaction by Vasella and co-workers[8] and the synthesis of *syn*-3,6-dihydro-1,2-oxazines through nitroso Diels–Alder cyclisation[5] have all benefited from this strategy.

The traditional method for the preparation or in situ generation of α-chloronitroso compounds involves the reaction of an oxime with chlorine,[9] *tert*-butyl hypochlorite,[10] or related electrophilic halogen precursors.[11] However, during the course of a synthetic program designed to explore the potential of the intramolecular variant of the nitrosoene reaction[12] using α-chloronitroso compounds,[13] competitive chloronium ion transformation of several olefinic oximes proved to be problematic. Indeed, this alternative mechanistic pathway involving the nucleophilic attack of an oxime onto a bridged cation has formed the basis of a useful alternative cyclisation method.[14]

Results and discussion

As a consequence of the this problem, it was necessary to invent a new method for the preparation of α-chloronitroso compounds that circumvented the use of an electrophilic halogen source. As outlined in Scheme 1, we reasoned that the reaction of a secondary nitronate anion (**1**) with oxalyl chloride would lead, via *O*-acylation and the subsequent capture of a chloride anion, to an intermediate (**2**) that would be predisposed to undergo a decarboxylative fragmentation reaction leading to the desired germinal chloronitroso compound (**3**). The initial *O*-acylation step finds precedent in the pioneering work of Zefirov and co-workers[15] on the [2,3] sigmatropic rearrangement of acyloxynitronic acids. Herein, we now report, in full detail,[16] on the practical implementation of this idea, together with a new and milder alternative variant.

Several important facets of this transformation were revealed in a series of preliminary experiments. Firstly, given that the isolation of a metallic nitronate salt is not an advisable practice,[17] it was important to examine a selection of bases and solvent systems for efficient generation of a reactive nitronate anion. The reaction sequence selected is shown in Scheme 2 and features hetero-Diels–Alder trapping of the product, 2-chloro-2-nitrosopropane (**4**), followed by hydrolysis to give the known isolable hydrochloride adduct (**5**).[18] Examination of the results in Table 1 reveals that the more charge separated potassium nitronates (entries 5 and 6) are superior to their lithium counterparts. The emergence of Schlosser's base as the

Received 29 June 2012. Accepted 6 September 2012. Published at www.nrcresearchpress.com/cjc on 17 December 2012.

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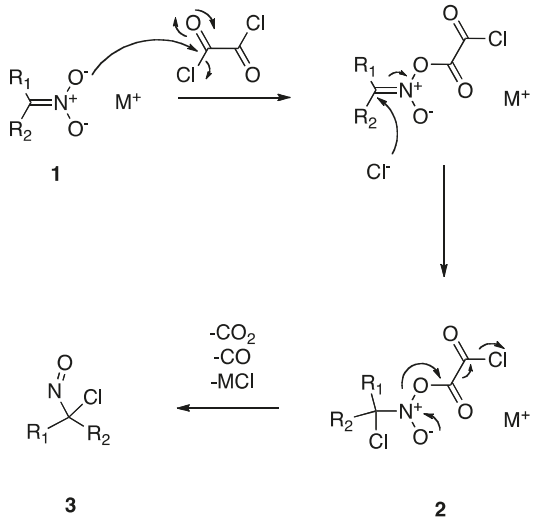
This article is part of a Special Issue dedicated to Professor Derrick Clive. Dedicated with respect to Professor Derrick L. J. Clive, an Imperial scholar, a Bartonian, and a meticulous chemist.

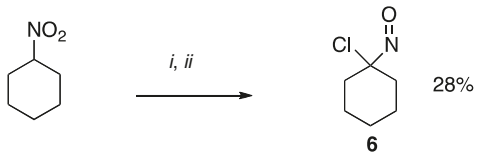
Scheme 1.



most successful is readily understood, since nitronate anion formation is a slow process subject to general base catalysis (2-nitropropane pK_a = 7.74, ratio at room temperature (rt) [$Me_2C{=}NO_2H$]/[Me_2CHNO_2] is 3×10^{-3}).[19] A second practical consideration was that a rapid single addition of oxalyl chloride to the preformed nitronate salt was necessary, since the product α-chloronitroso compound could undergo a subsequent reaction with the nitronate salt to form an oxime, probably by a single electron transfer process.[16]

Even though volatile 2-chloro-2-nitrosopropane was not isolated in these reactions, the results indicate that it can be formed in at least a 85% yield. Adduct **5** could also be isolated in a 55% yield when 1-nitrocyclohexane was used as substrate, and it was also possible to prepare and isolate pure 1-chloro-1-nitrosocyclohexane (**6**) using this method, albeit in a low yield (eq. [1]).

[1]



Reagents: (*i*) *n*-BuLi, KO-*t*-Bu, Et_2O, 0 °C; (*ii*) oxalyl chloride (2.5 equiv), 15 min.

The use of the previous protocol was also tested using three further cyclic dienes and a further comparison was made between 2-nitropropane and 1-nitrocyclohexane as geminal chloronitroso precursors. The results are shown in Table 2 and reveal that selection of the smaller reagent may be beneficial in the more hindered situations (Table 2, entry 2). The observed diastereoselectivity and higher yield with cyclohepta-3,5-diene-1-ol (Table 2, entry 3) may be a consequence of assisted hydrogen bonding from the hydroxyl group to the nitrosodienophile. Such bicyclic adducts have proven to be of value in the synthesis of complex cyclopentanoids,[6b] inositols,[20] and tropane[21] alkaloids.

While the above study had established the viability of this novel functional group transformation, it was nevertheless

Scheme 2. Reagents: (*i*) base (1.0 equiv), solvent, 0 °C; (*ii*) oxalyl chloride (5.0 equiv); (*iii*) filtration; (*iv*) MeOH, 2 mol/L HCl.

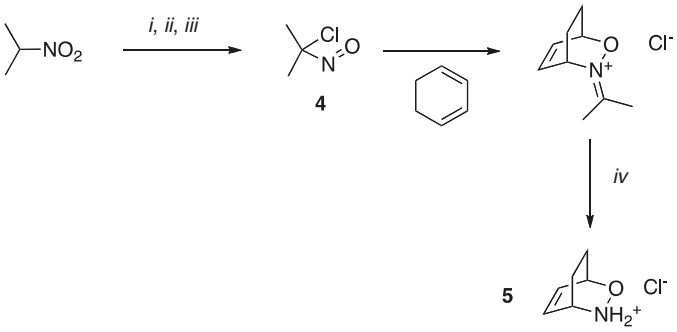


Table 1. Optimization of Scheme 2.

		Solvent (yield of **5**, %)		
Entry	Base	Et_2O	THF	Toluene
1	LDA	23	4	21
2	LiHMDS	35	37	3
3	*n*-BuLi	41	23	16
4	NaH	—	—	—
5	KO-*t*-Bu	60	51	66
6	KO-*t*-Bu/*n*-BuLi	82	56	85

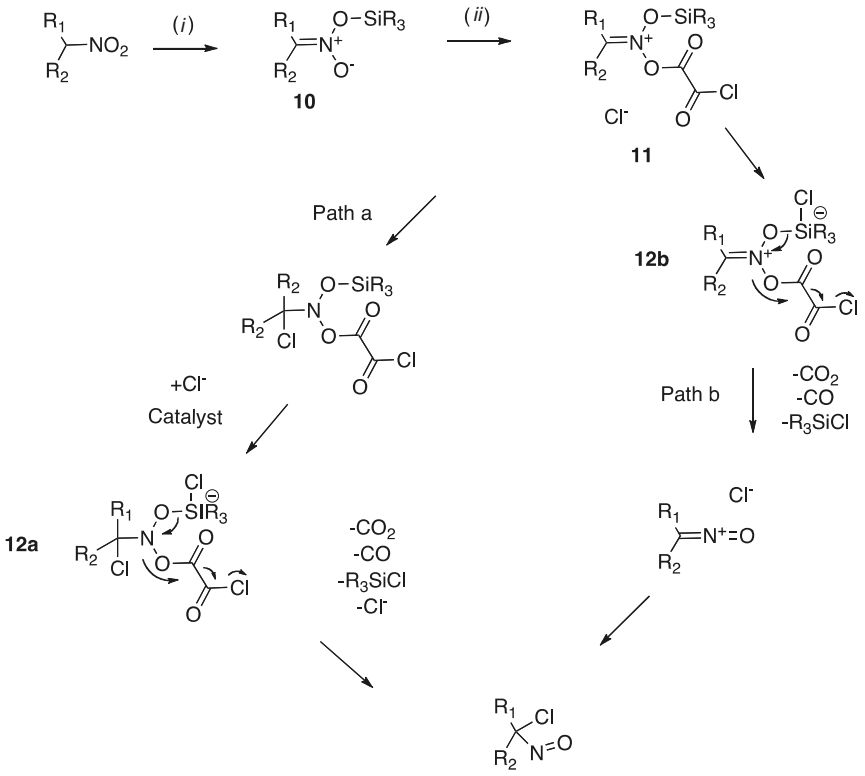
Note: THF, tetrahydrofuran; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide.

Table 2. Substrates synthesized by the method in eq. [1].

				Yield (%)	
Entry	Diene	Compound	Isolated cycloadduct	**4**	**6**
1		**7**		38	34
2		**8**		40	16
3		**9**		52	50

clear that, in terms of chemoselectivity for more sensitive and highly functionalized substrates, the use of such strong bases for nitronate anion formation was not desirable. In particular, substrates prone to base induced dehydrohalogenation or enolate anion formation were problematic. We therefore reasoned, as shown in Scheme 3, that prior formation of a silyl nitronate[22] could be advantageous. Thus, reaction of **10** with

Scheme 3. Reagents: (*i*) R_3SiCl, base; (*ii*) oxalyl chloride.



oxalyl chloride could then generate an intermediate (**11**) and chloride anion capture could then occur, either on carbon (Scheme 3, path a) or via formation of an initial silicon–ate complex (Scheme 3, path b) to form analogous intermediates for decarboxylative fragmentation.

The results for a series of optimization experiments using nitrocyclododecane (**13**) are presented in Table 3 and involve a sequential sequence of in situ silyl nitronate (**14**) generation at room temperature for 30 min followed by cooling to 0 °C, the addition of of oxalyl chloride (2.5 equiv), and stirring for 2 min (Scheme 4).

Substrate **13** was chosen because the product, α-chloronitroso cyclododecane (**15**), proved to be a nonvolatile, deep blue, and highly crystalline product whose monomeric nature was confirmed by a single crystal X-ray diffraction study.[23] The reaction conditions used for generation of the various silyl nitronates (**14**) are essentially based on those developed by Palomo and co-workers.[24] As highlighted earlier, deprotonation of a nitro compound may be slow and is not trivial, with bases such as triethylamine (Table 3, entry 6) and DABCO (Table 3, entry 7) unreactive, with only 1,8-diazabicycloundec-7-ene (DBU) proving to be essential and 1.5 molar equiv proving to be optimum (Table 3, entries 12–14). The most crucial variable proved to be the nature of the organosilicon group (Table 3, entries 1–4), which has to provide a compromise between the ease of the formation and stability of the silyl nitronate against its subsequent reactivity in forming an ate complex with chloride anion to facilitate fragmentation. A comparison of entries 1–5 (Table 3) clearly reveals that the TBDMS group emerges as the most successful. To some extent, a parallel can be drawn with the relative rates of acid hydrolysis of silyl ethers[25] (Me_3Si (1) < TBDMS (10 000) < TIPS (700 000) < TBDPS (5 000 000)) inasmuch as the TMS group is much too labile and the TIPS and TBDPS groups are much too hindered in terms of nucleophilic attack at silicon. It

Table 3. Optimization of Scheme 4.

Entry	Base (equiv)	Silyl chloride (equiv)	Solvent	Yield of **15** (%)
1	DBU (1.2)	TMS (2)	CH_2Cl_2	9
2	DBU (1.2)	TBDPS (2)	CH_2Cl_2	40
3	DBU (1.2)	TIPS (2)	CH_2Cl_2	50
4[a]	DBU (1.2)	TBDMS (2)	CH_2Cl_2	65
5	DBU (1.2)	TBDMS (2)	CH_2Cl_2	72
6	Et_3N (1.2)	TBDMS (2)	CH_2Cl_2	0[b]
7	DABCO (1.2)	TBDMS (2)	CH_2Cl_2	0[b]
8	DBU (1.2)	TBDMS (2)	Hexane	66
9	DBU (1.2)	TBDMS (2)	THF	48
10	DBU (1.2)	TBDMS (2)	Et_2O	65
11	DBU (1.2)	TBDMS (2)	CH_2Cl_2[c]	70
12	DBU (1.5)	TBDMS (2)	CH_2Cl_2	80
13	DBU (2.0)	TBDMS (2)	CH_2Cl_2	76
14	DBU (1.0)	TBDMS (2)	CH_2Cl_2	65

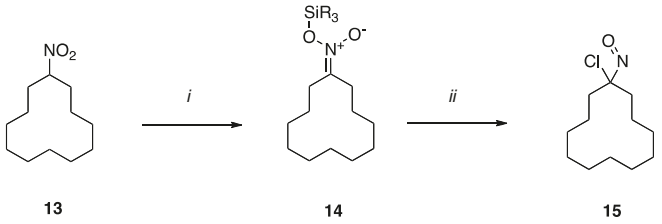
Note: DBU, 1,8-diazabicycloundec-7-ene; TMS, tetramethylsilane; TBDPS, *tert*-butyldiphenylsilyl; TIPS, triisopropylsilyl; TBDMS, *tert*-butyldimethylsilyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; THF, tetrahydrofuran.

[a]Deprotonation at 0 °C.

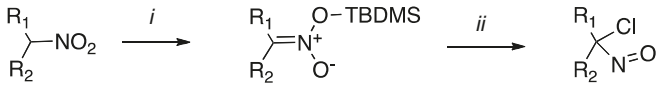
[b]No reaction.

[c]Catalytic dimethylformamide (DMF).

Scheme 4. Reagents: (*i*) base, R_3SiCl, solvent, 30 min, room temperature (rt); (*ii*) oxalyl chloride (2.5 equiv), 0 °C, 2 min.



Scheme 5. Reagents: (*i*) DBU (1.5 equiv), TBDMSCl (2.0 equiv), CH_2Cl_2, 30 min, room temperature (rt); (*ii*) oxalyl chloride (2.5 equiv), 0 °C, 2 min.

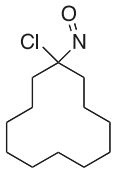
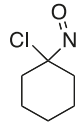
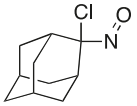
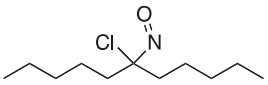
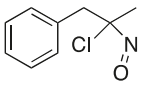
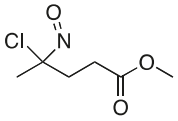
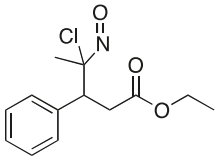
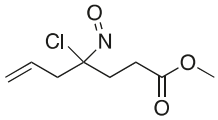
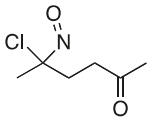
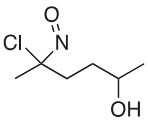


is important to note that, in the absence of a silicon electrophile, α-chloronitroso compounds were not formed, and that, in terms of solvent, dichloromethane, hexane, and diethyl ether (Table 3, entries 5, 8, and 10) can all be used. A simple NMR experiment in CD_2Cl_2 confirmed the optimum conditions noted in entry 12 (Table 3) inasmuch as complete consumption of both nitrocyclododecane and its TBDMS-protected nitronate was observed. We also note parenthetically that oxalyl chloride may be replaced by ethyl chlorooxoacetate, which afforded **15** in a slightly lower yield (52%). Initial experiments using ethyl chloroformate or the Vilsmeier reagent were, however, unsuccessful. A series of secondary nitro compounds was then subjected to the experimental conditions delineated in Scheme 5. Examination of the results (Table 4) reveals that, with simple acyclic substrates (Table 4, entries 4 and 5) and also with the macrocyclic ring (Table 4, entry 1), excellent yields can be isolated, whereas reactions containing six-membered ring systems (Table 4, entries 2 and 3) proceed with a more moderate yield. Remote ester functionality (Table 4, entries 6–8) and simple alkenes (Table 4, entry 8) are tolerated, although conversion of a secondary nitro ketone (Table 4, entry 9) proceeded with a much lower yield. Not unexpectedly, the selection of a TBDMS-protected alcohol (Table 4, entry 10) led to concomitant deprotection, but once again, conversion of the nitro group to the geminal chloronitroso moiety proceeded with an excellent yield. The superiority of the silyl nitronate variant over the initial method involving potassium *tert*-butoxide in the formation of a metallic nitronate salt is readily appreciated by comparison of the isolated yields for the two methods, especially for those more sensitive substrates prone to dehydrohalogenation (Table 4, entry 5) or competing enolate anion formation (Table 4, entries 6 and 9).

Conclusion

In summary, the foregoing study has provided proof of a concept for this novel functional group interconversion via nitronate anion chemistry. The mild reaction conditions employed using in situ generation of a silyl nitronate are especially useful in terms of functional group compatibility and will hopefully encourage the exploration of the richly adorned

Table 4. Substrates synthesized by the method in Scheme 5.

Entry	Product		Yield (%)
1	**15**		80
2	**6**		47 (28)[a]
3	**16**		58
4	**17**		78
5	**18**		80 (26)[a]
6	**19**		72 (28)[a]
7	**23**		69
8	**20**		73
9	**21**		23 (0)[a]
10	**22**		85[b]

[a]Yield using potassium nitronate and oxalyl chloride, deprotonated by KO-*t*-Bu.

[b]Substrate, *tert*-butyldimethylsilyl (TBDMS) protected nitroalcohol.

geminal chloronitroso unit in more complex molecular environments.

Experimental

General experimental

All chemicals used were purchased commercially and purified by literature methods.[26] Experiments involving moisture- and (or) air-sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen. Diethyl ether, CH_2Cl_2, hexane, tetrahydrofuran, and toluene were purified by alumina/copper catalyst columns. Flash chromatography was performed on silica gel (230–400 mesh). Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using ultraviolet (UV) radiation at 254 nm. Further visualization was possible by staining with a basic solution of potassium permanganate or a phosphomolybdic acid solution. Infrared (IR) spectra were recorded on a PerkinElmer 1605 Fourier transform (FT)-IR spectrometer. Mass spectra were recorded on Micromass 70-ES Magnetic Sector spectrometer (VG ZAB) by electron impact (EI), chemical ionization (CI), or atmospheric pressure chemical ionization (ECPI (positive model)). The ^{1}H NMR spectra were measured at 600 MHz on a Bruker A600, at 500 MHz on a Bruker Avance 500, and at 400 MHz on a Bruker 400. The ^{13}C NMR spectra were measured at 150 MHz on a Bruker A600, at 125 MHz on a Bruker Avance 500, and at 100 MHz on a Bruker 400. The spectra were obtained from solution in deuterated water, methanol, water, or chloroform, with TMS as internal standard. The residual protic solvents were 4.79 ppm for D_2O, 3.31 and 49.0 ppm for MeOD, and 7.27 and 77.2 ppm for $CDCl_3$. Compounds **6**, **7**, **8**, and **9**,[16]nitrocyclododecane,[27] 2-nitroadamantane, 6-nitroundecane,[28] 2-nitropropylbenzene,[29] methyl 4-nitropentanoate, methyl 4-nitrohept-6-enoate, 5-nitrohexane-2-one, 5-nitrosohexan-2-ol, and *tert*-butyldimethyl-(1-methyl-4-nitro-pentyloxy)silane[30] were synthesized according to and in agreement with the literature procedures.

Experimental procedures

Ethyl 4-nitro-3-phenylpentanoate

To a solution of 2-nitroethane (1.80 g, 24 mmol) and ethyl cinnamate (3.52 g, 20 mmol) in acetonitrile (10 mL), DBU (3.05 g, 20 mmol) was added at room temperature at once. After stirring the solution for 24 h, water (50 mL) was added dropwise over 5 min. The mixture was acidified with 2 mol/L HCl (20 mL) and extracted with Et_2O (3 × 50 mL).The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (petroleum spirit/Et_2O 9:1) afforded the desired product (2.88 g, 48%). IR (neat, cm^{-1}): 3066, 2986, 1734, 1549, 1455, 1389, 1177, 702. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.10 (3H, t, J = 7.2 Hz, CH_3), 1.35 (3H, d, J = 6.7 Hz, CH_3), 2.66 (1H, dd, J = 15.6, 4.9 Hz, CH_2), 2.78 (1H, dd, J = 15.6, 10.0 Hz, CH_2), 3.62–3.69 (1H, m, CH), 3.94–4.05 (2H, m, CH_2), 4.69–4.75 (1H, m, CH), 7.17–7.20 (2H, m, CH_{Ar}), 7.26–7.35 (3H, m, CH_{Ar}). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1 (CH_3), 17.9 (CH_3), 35.9 (CH_2), 46.5 (CH_3), 60.8 (CH_2), 87.2 (CH), 128.1 (CH), 128.3 (2CH), 129.2 (2CH), 137.6 (C), 170.6 (CO). MS *m/z*: 252 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{13}H_{18}NO_4$: 252.1236; found: 252.1230.

General experimental procedure for *gem*-chloronitroso preparation

To a cooled (0 °C) solution of nitro compound (1.00 mmol) in anhydrous CH_2Cl_2 (3 mL) under a N_2 atmosphere, DBU (0.22 mL, 1.5 mmol) and chloro-*tert*-butyldimethylsilane (TBDMSCl) (0.30 g, 2.0 mmol) were added successively. After stirring for 30 min at rt, the mixture was cooled at 0 °C and oxalyl chloride (0.21 mL, 2.5 mmol) was added at once. The evolution of gas occurred and a deep blue reaction mixture was formed. (Caution: The evolution of gas could be very vigorous!) After stirring the solution for a further 2 min, petroleum spirit (20 mL) and water (5 mL) were then added consecutively dropwise over 1 min. The aqueous layer was extracted with petroleum spirit (2 × 10 mL), the combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure using a cold bath, and protected from direct light. The isolated material was purified by flash chromatography on silica gel, affording the desired product.

1-Chloro-1-nitrosocyclododecane (15)[31]

Prepared from nitrocyclododecane (213 mg, 1.00 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (185 mg, 80%) as a deep blue solid; mp (petroleum spirit) 55–56 °C (lit.[31] mp 55–57 °C). IR (neat, cm^{-1}): 2928, 2861, 1577, 1560, 1469, 1445, 726. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (14H, s, CH_2), 1.62–1.50 (2H, m, CH_2), 1.85–1.69 (4H, m, CH_2), 2.49–2.39 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3 (CH_2), 22.2 (CH_2), 22.7 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 32.7 (CH_2), 119.0 (C). MS *m/z*: 232 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{12}H_{23}NO^{35}Cl$: 232.1468; found: 232.1474. Anal. calcd for $C_{12}H_{22}ClNO$ (%): C 62.19, H 9.57, N 6.04; found: C 62.32, H 9.77, N 5.99.

2-Chloro-2-nitrosoadamantane (16)[32]

Prepared from 2-nitroadamantane (423 mg, 2.50 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (320 mg, 58%) as a deep blue oil. IR (neat, cm^{-1}): 2914, 2865, 1561, 1454. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97–1.83 (6H, m, CH_2, CH), 2.12–1.98 (4H, m, CH_2, CH), 2.37–2.29 (2H, m, CH_2, CH), 2.47 (2H, s, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.0, 27.1, 34.5, 34.7, 37.1, 37.7 (CH_2, CH), 114.4 (C). MS *m/z*: 166 ([M – Cl]$^+$), 167 ([M – Cl]$^+$), 168 ([M – Cl]$^+$), 200 ([M + H]$^+$), 201 ([M + H]$^+$), 202 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{10}H_{15}NO^{35}Cl$: 200.0848; found: 200.0842.

6-Chloro-6-nitrosoundecane (17)[32]

Prepared from 6-nitroundecane (503 mg, 2.50 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (430 mg, 78%) as a deep blue oil. IR (neat, cm^{-1}): 2955, 2931, 2868, 1579, 1464, 1380, 721. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83–0.91 (6H, m, CH_3), 0.91–1.00 (2H, m, CH_2), 1.21–1.39 (10H, m, CH_2), 2.23–2.34 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9 (CH_2), 22.3 (CH_2), 22.8 (CH_2), 31.6 (CH_2), 37.6 (CH_2), 122.7 (C). MS *m/z*: 220 ([M + H]$^+$), 221 ([M + H]$^+$), 222 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{11}H_{23}NO^{35}Cl$: 220.1468; found: 220.1471.

2-Chloro-2-nitrosopropylbenzene (18)[33]

Prepared from 2-nitropropylbenzene (165 mg, 1.00 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (147 mg, 80%) as a deep blue oil. IR (neat, cm^{-1}): 3033, 2928, 1713, 1583, 1563, 1496, 1455, 1447, 1373, 1087, 736, 700. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.77 (3H, m, CH_3), 3.64–3.74 (2H, m, CH_2), 7.15–7.22 (2H, m, CH), 7.28–7.35 (3H, m, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7 (CH_3), 44.4 (CH_2), 115.5 (C), 127.6 (CH), 128.3 (CH), 128.7 (CH), 130.9 (CH), 133.6 (C). MS *m/z*: 153 ([M – NO]$^+$), 154 ([M – NO]$^+$), 155 ([M – NO]$^+$). HR-MS *m/z* ([M – NO]$^+$) calcd for $C_9H_{10}{}^{35}Cl$: 153.0471; found: 153.0469.

Methyl 4-chloro-4-nitrosopentanoate (19)

Prepared from 4-methyl-4-nitropentanoate (161 mg, 1.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (127 mg, 72%) as a deep blue oil. IR (neat, cm^{-1}): 2955, 1737, 1585, 1563, 1438, 1197, 1174. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.80 (3H, s, CH_3), 2.14–2.24 (1H, m, CH_2), 2.36–2.46 (1H, m, CH_2), 2.57–2.67 (1H, m, CH_2), 2.88–2.98 (1H, m, CH_2), 3.67 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.2 (CH_3), 28.5 (CH_2), 33.4 (CH_2), 51.9 (CH_3), 115.5 (C), 172.3 (CO). MS *m/z*: 149 ([M – NO]$^+$) 150 ([M – NO]$^+$), 151 ([M – NO]$^+$). HR-MS *m/z* ([M – NO]$^+$) calcd for $C_6H_{10}{}^{35}ClO_2$: 149.0364; found: 149.0368.

Methyl 4-chloro-4-nitrosohept-6-enoate (20)

Prepared from methyl 4-nitrohept-6-enoate (187 mg, 1.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (150 mg, 73%) as a deep blue oil. IR (neat, cm^{-1}): 2954, 1737, 1582, 1563, 1437, 1199, 1174. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.96–2.06 (1H, m, CH_2), 2.30–2.40 (1H, m, CH_2), 2.63–2.73 (1H, m, CH_2), 3.26–3.04 (3H, m, CH_2), 3.68 (3H, s, CH_3), 5.16–5.25 (2H, m, CH_{allyl}), 5.54–5.66 (1H, m, CH_{allyl}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0 (CH_2), 32.0 (CH_2), 41.7 (CH_2), 51.9 (CH_3), 119.1 (C), 121.2 (CH_2), 129.4 (CH), 172.3 (CO). MS *m/z*: 206 ([M + H]$^+$), 207 ([M + H]$^+$), 208 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_8H_{13}NO_3{}^{35}Cl$: 206.0584; found: 206.0589.

5-Chloro-5-nitrosohexan-2-one (21)

Prepared from 5-chloro-5-nitrohexan-2-one (290 mg, 2.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (75 mg, 23%) as a deep blue oil. IR (neat, cm^{-1}): 2933, 1718, 1584, 1564, 1424, 1365, 1167. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.84 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.24–2.34 (1H, m, CH_2), 2.46–2.63 (2H, m, CH_2), 2.89–2.99 (1H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6 (CH_3), 30.0 (CH_2), 32.0 (CH_2), 38.4 (CH_3), 116.2 (C), 206.2 (CO).

Ethyl 4-chloro-4-nitroso-3-phenylpentanoate (23)

Prepared from ethyl 4-nitro-3-phenylpentanoate (251 mg, 1.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (185 mg, 69%) as a deep blue oil. IR (neat, cm^{-1}): 2982, 1733, 1582, 1455, 1374, 1160. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.04 (3H, t, J = 7.2 Hz, CH_3), 1.47 (3H, s, CH_3), 2.18 (1H, dd, J = 16.1, 4 Hz, CH_2), 2.79 (1H, dd, J = 16.1, 10.8 Hz, CH_2), 3.92 (2H, m, CH_2), 5.00 (1H, dd, J = 10.8, 4.0 Hz, CH), 7.31–7.38 (3H, m, CH_{Ar}), 7.43–7.47 (2H, m, CH_{Ar}). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1 (CH_3), 23.7 (CH_3), 35.5 (CH_2), 47.4 (CH_3), 60.8 (CH_2), 119.5 (C), 128.3 (CH), 128.6 (2CH), 129.9 (2CH), 136.5 (C), 170.7 (CO). MS *m/z*: 239 ([M – NO]$^+$), 240 ([M – NO]$^+$), 241 ([M – NO]$^+$). HR-MS *m/z* ([M – NO]$^+$) calcd for $C_{13}H_{16}{}^{35}ClO_2$: 239.0839; found: 239.0845.

5-Chloro-5-nitrosohexan-2-ol (22)

Prepared from 5-chloro-5-nitrohexan-2-one (290 mg, 2.00 mmol), purification (petroleum spirit/Et_2O 90:10) produced the corresponding chloronitroso product (140 mg, 85%) as a deep blue oil. IR (neat, cm^{-1}): 3308, 2969, 2932, 1582, 1445, 1375, 1134, 1032, 931. ^1H NMR (600 MHz, C_6D_6) δ: 0.82–0.88 (3H, m, CH_3), 0.97–1.10 (1H, m, CH_2), 1.41 (3H, s, CH_3), 1.91–2.01 (1H, m, CH_2), 2.57–2.67 (1H, m, CH_2), 3.30–3.40 (1H, m, CH_2). ^{13}C NMR (150 MHz, C_6D_6) δ: 23.5 (CH_3), 24.1 (CH_3), 33.0 (CH_2), 35.2 (CH_2), 67.0 (CH), 117.4 (C). MS *m/z*: 166 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_6H_{13}NO_2{}^{35}Cl$: 166.0635; found: 166.0625.

Acknowledgements

The authors would like to thank Dr. A.E. Aliev for his collaboration on the NMR study and Dr. S. Coles for his collaboration on the X-ray diffraction. The authors would also like to thank Dr.Dr. R. Hay-Motherwell for her generous permission to finance this study.

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Enantioselective synthesis of 3-substituted tryptamines as core components of central nervous system drugs and indole natural products

Stephen Hanessian and Elia J.L. Stoffman

Abstract: Application of the MacMillan iminium ion Michael and Friedel–Crafts type reactions to γ-amino α,β-unsaturated butanals led to the corresponding β-substituted butanals in good yields and high enantioselectivities. The products could be useful intermediates in the synthesis of indole-based central nervous system (CNS) drugs and natural products.

Key words: iminium ion alkylation, indole natural products, 3-substituted indoles.

Résumé : L'utilisation d'ions iminium de MacMillan dans des réactions de type Michael ou Friedel–Crafts sur des γ-aminobutanals α,β-insaturés conduit à la formation des butanals β-substitués correspondants, avec de bons rendements et des énantiosélectivités élevés. Ces produits pourraient être des intermédiaires utiles dans la synthèse de produits naturels et de médicaments pour le système nerveux central (CNS) à base d'indole.

Mots-clés : alkylation d'un ion iminium, produits naturels à base d'indole, indoles avec substitution en position 3.

[Traduit par la Rédaction]

Introduction

The tryptamine moiety is found in a number of drugs as well as pharmacologically active alkaloids[1] that use L-tryptophan as a biosynthetic precursor.[2] Drug prototypes with demonstrated activity against a host of central nervous system (CNS)-related targets and containing various azacyclic rings attached to indoles are of interest. For example, NXN274 and naratriptan[3,4] are known to act on the serotonergic (5-hydroxytryptamine or 5-HT) receptors (Fig. 1).

Gelliusine E,[5] a member of the diindole methane family of alkaloids, has generated attention[6] owing to the novel biological profile of this class of symmetrical and nonsymmetrical bisindoles.

Results and discussion

In connection with a project aimed at exploiting a practical asymmetric synthesis of NXN274, we recently reported[3] the synthesis of an advanced intermediate, *S*-(–)-**1**, using MacMillan's iminium activation of α,β-unsaturated aldehydes as a means of stereocontrolled and enantioselective branching (Scheme 1).[7]

Although examples of Michael and Friedel–Crafts type additions to α,β-unsaturated aldehydes with alkyl and related substituents at the γ-position were known from the MacMillan group[7a,7e] and others,[8] we required an α,β-unsaturated butanal harbouring a functionalized amino group at the γ-carbon, such as **3**. We now report on the details of this approach toward the stereoselective synthesis of α-branched 3-substituted indoles (**4**), and its extension to other synthetically useful substrates.

The synthesis of the desired (*S*)-(–)-**1** is outlined in Scheme 2. The treatment of *N*-Boc, *N*-methyl acetaldehyde **5** with triethylphosphonoacetate under standard conditions followed by reduction with diisobutylaluminum hydride (DIBAL-H) led to allylic alcohol **6**, which was oxidized to the aldehyde **3** with the Dess–Martin periodinane reagent in an excellent yield. The activation of **3** with the (*R*,*R*)-MacMillan catalyst,[7a] followed by addition of 5-bromoindole, afforded the adduct **7** in a quantitative yield. Reduction to the alcohol **8** and mesylation or tosylation to **9**, followed by cleavage of the *N*-Boc group and treatment of the product with potassium carbonate in a mixture of tetrahydrofuran (THF) and dimethylformamide (DMF) as the solvent led to the target compound, (*S*)-(–)-**1**, in an excellent yield. The absolute configuration was confirmed by single crystal X-ray analysis (see ref. 3 of the Supplementary data), and stereochemical purity (88% enantiomeric excess (ee)) was established by chiral HPLC analysis.

The suitability of **3** as a Michael acceptor in the MacMillan organocatalytic addition of 5-bromoindole to give β-branched aldehydes such as **7** with high enantioselectivity led us to explore the same reactions with other N substituents.

The results shown in Table 1 indicate that a variety of N substituents can be used in the original reaction with excellent enantioselectivities, which did not seem to vary significantly with less sterically bulky protecting groups on nitrogen (Table 1, entry 3) or when groups with a stronger

Received 12 June 2012. Accepted 24 July 2012. Published at www.nrcresearchpress.com/cjc on 20 December 2012.

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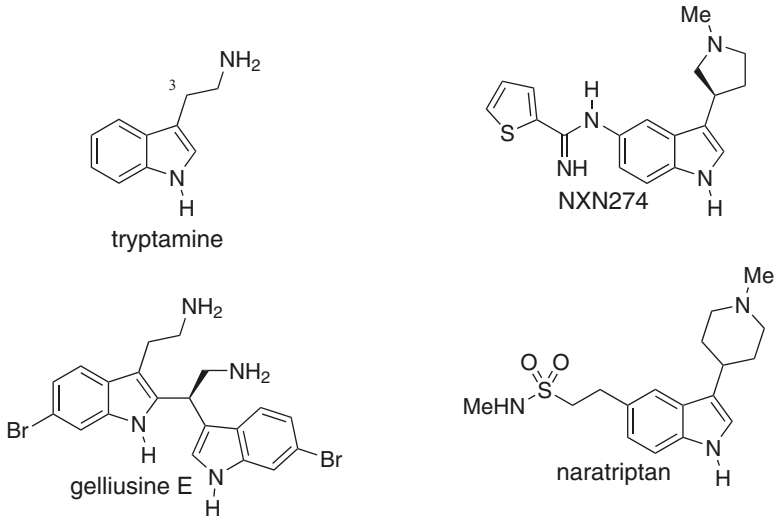
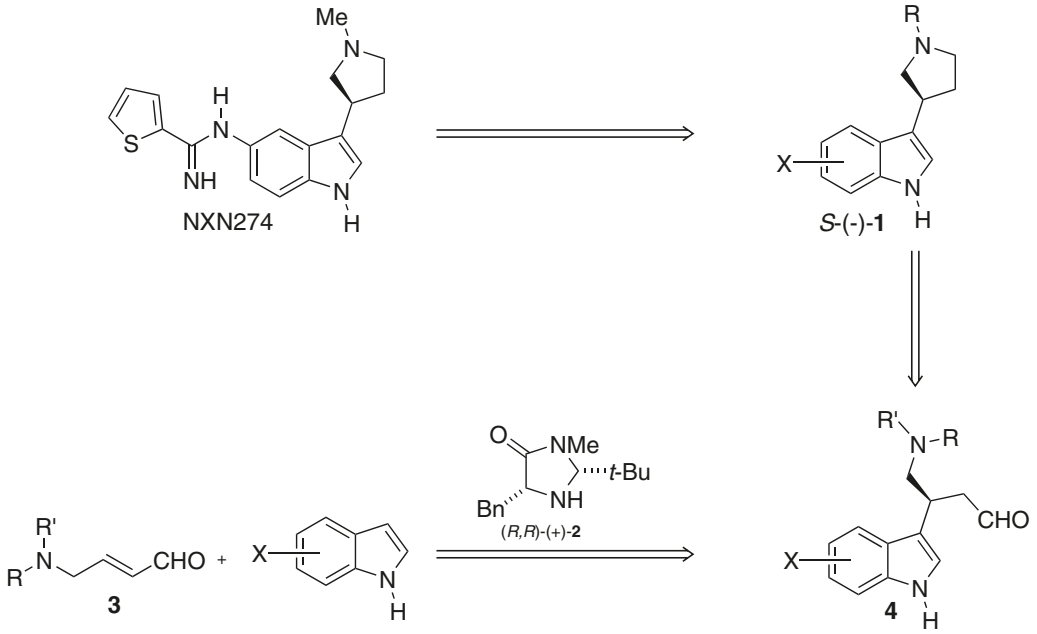
This article is part of a Special Issue dedicated to Professor Derrick L. J. Clive and wishing him the best in life and in chemistry.

Fig. 1. Examples of 3-substituted tryptamines as drugs or natural products.



Scheme 1. Retrosynthetic analysis of NXN274.



electron-withdrawing capability were introduced (Table 1, entry 2). However, when the bulkier bis-protected substrates were used, longer reaction times were necessary (Table 1, entries 4 and 5).

The synthesis of the bis-protected aldehyde **15** (Table 1, entries 4 and 5) proceeded smoothly through a cross-metathesis approach (Scheme 3). Thus, anisaldehyde (**10**) was reductively aminated with allylamine (**11**) to give *N*-allyl-4-methoxybenzylamine (**12**), and this was protected as the *tert*-butylcarbamate **13**. Cross metathesis with methyl acrylate in the presence of the Grubbs II catalyst gave the methyl ester **14**, which was reduced to the corresponding alcohol before oxidation by the Parikh–Doering method to the bis-protected aminoaldehyde **15**.

We then turned our attention to α,β-unsaturated aldehydes containing γ- and δ-amino groups protected as the *tert*-butylcarbamates (Scheme 4).

The use of aldehyde **16a**[9] under the conditions established in Table 1 (vide supra) led to transformation of the aldehyde to *N*-Boc–pyrrole, without incorporation of the indole moiety. However, the homologated aldehyde **16b**[10] underwent smooth conversion to the cyclized *N*-Boc enamine **17**, which could be converted to the *O*-methyl hemiaminal **18** under acid catalysis. The latter could be converted to the achiral naratriptan precursor (**19**) under conditions reported by Leonard and Woerpel[11] (BF_3–OEt_2, Et_3SiH), or by hydrogenation over Rh catalyst in the presence of AcOH.[12] In the absence of acetic acid, neither *O*-methyl hemiaminal **18**

Scheme 2. Synthesis of *S*-(–)-**1**. Reagents and conditions: (*a*) (*i*) triethylphosphonoacetate, NaH, THF, room temperature (rt), 30 min; (*ii*) DIBAL-H, THF, –78 °C, 30 min, 54% (two steps); (*b*) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 89%; (*c*) 5-bromoindole, (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one, trifluoroacetic acid (TFA), *i*-PrOH, CH_2Cl_2, –78 °C, 36 h, quant.; (*d*) $NaBH_4$, MeOH, rt, 2 h; (*e*) R = Me, MsCl, CH_2Cl_2, Et_3N, 0 °C to rt, 16 h, 80% (2 steps); R = *p*-tolyl, TsCl, CH_2Cl_2, Et_3N, 0 °C to rt, 16 h, 70% (two steps); (*f*) (*i*) HCl, 1,4-dioxane, 0 °C to rt, 1.5 h; (*ii*) K_2CO_3, THF–DMF, rt, 24 h, quant. for both sulfonates.

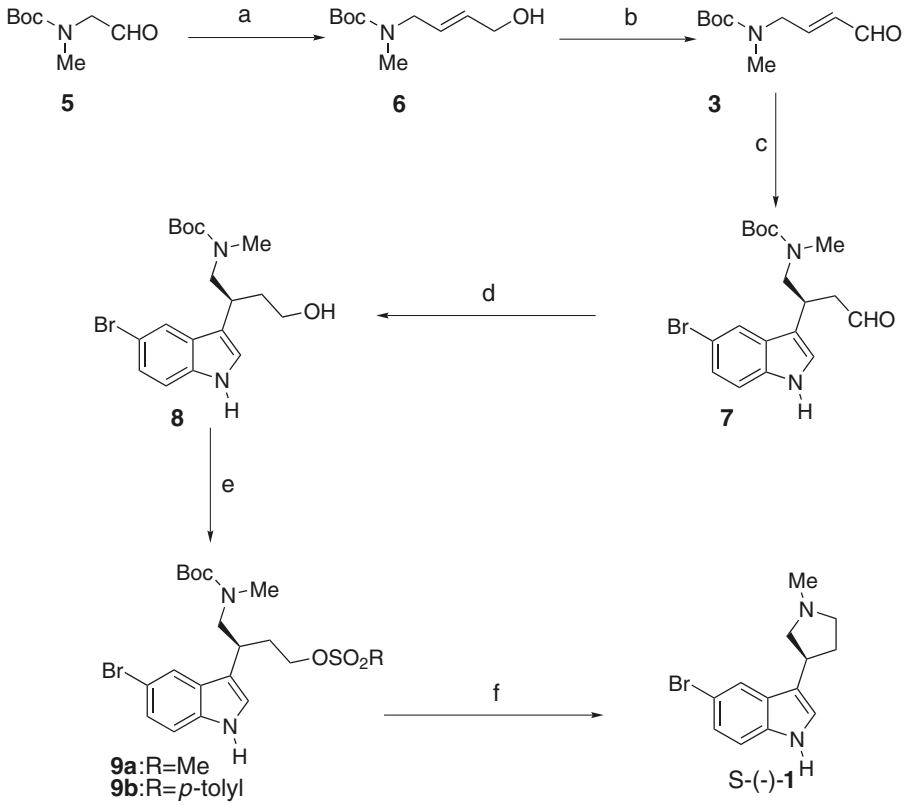
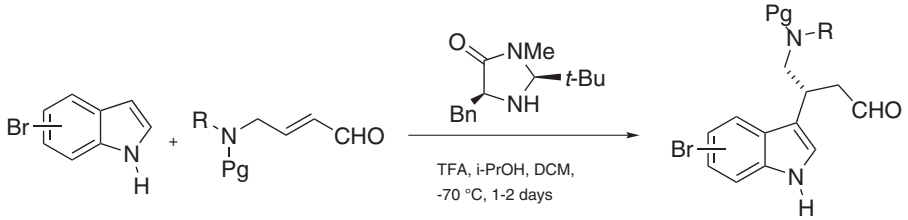


Table 1. Organocatalytic MacMillan indole alkylation using nitrogen-containing aldehydes.



Entry	Pg	R	Br position	Yield (%)[a]	ee (%)[b]	Time (days)
1	Boc	Me	5	Quant.	82	1
2	Bus	Me	5	89[c]	92	1
3	COOMe	Me	5	97	91	1
4	Boc	PMB	5	80	88	2
5	Boc	PMB	6	65 (83)[d]	81	2

Note: PMB, *p*-methoxybenzyl ether; quant., quantitative.

[a]Pure isolated yield unless otherwise indicated.

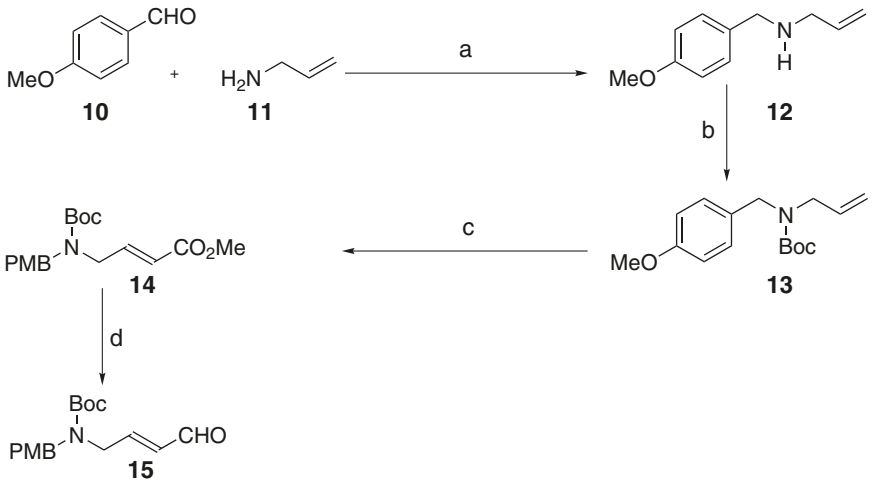
[b]Based on chiral HPLC analysis of the corresponding alcohols obtained by $NaBH_4$ reduction. The opposite enantiomer was obtained by running the reaction using the enantiomeric MacMillan catalyst.

[c]Pure isolated material (61%) and 28% in a mixture with starting aldehyde as determined by ^1H NMR.

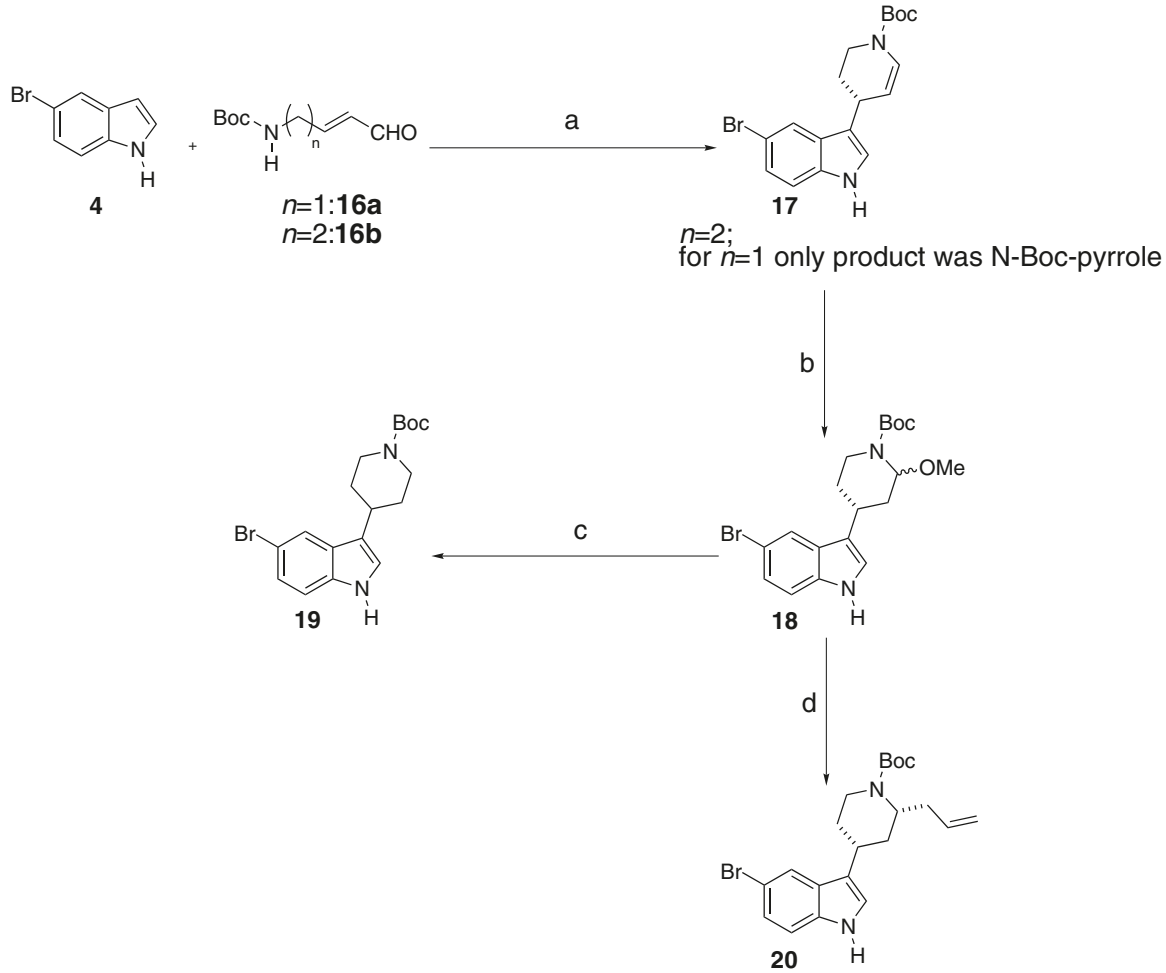
[d]Corrected for recovered 6-bromoindole.

nor enamine **17** were reduced by catalytic hydrogenation using either Rh-on-carbon or Crabtree's catalyst[13] at 8 atm (1 atm = 101.325 kPa) of hydrogen for 24 h. The treatment of **18** with allyltrimethylsilane in the presence of BF_3–OEt_2[11] afforded the 2-allyl naratripan analog **20**, an asymmetric naratriptan analog.

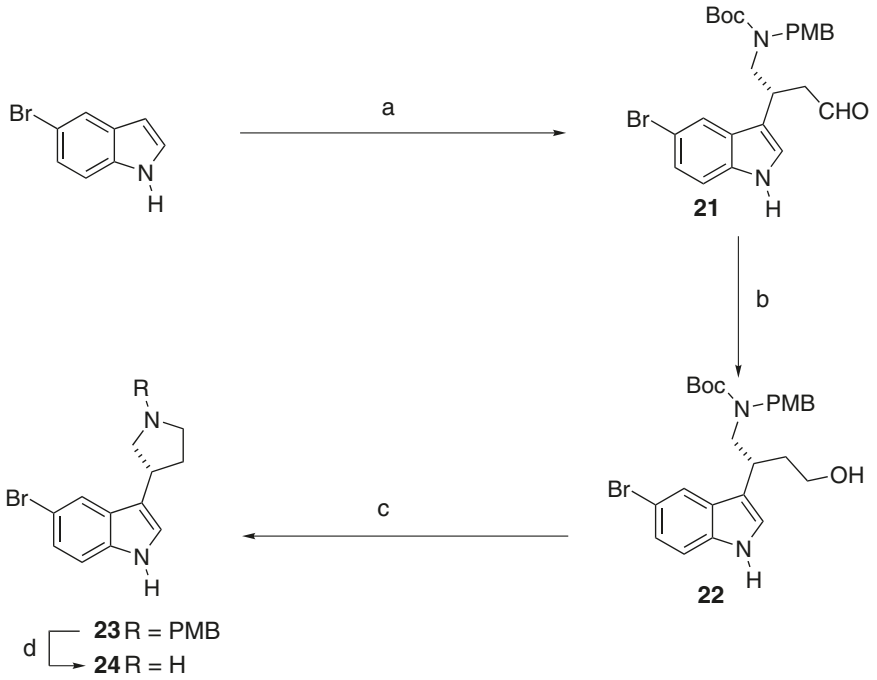
Scheme 3. Synthesis of bis-protected aminoaldehyde **15**. Reagents and conditions: (*a*) (*i*) $MgSO_4$, dichloromethane (DCM); (*ii*) $NaBH_4$, MeOH, 4 Å molecular sieves, 54% (two steps); (*b*) Boc_2O, THF, 50 °C, 91%; (*c*) methyl acrylate, Grubbs II, DCM, 52%; (*d*) (*i*) DIBAL-H, PhMe, –78 °C, 52%; (*ii*) SO_3-pyridine, triethylamine (TEA), dimethyl sulfoxide (DMSO), DCM, 74%.



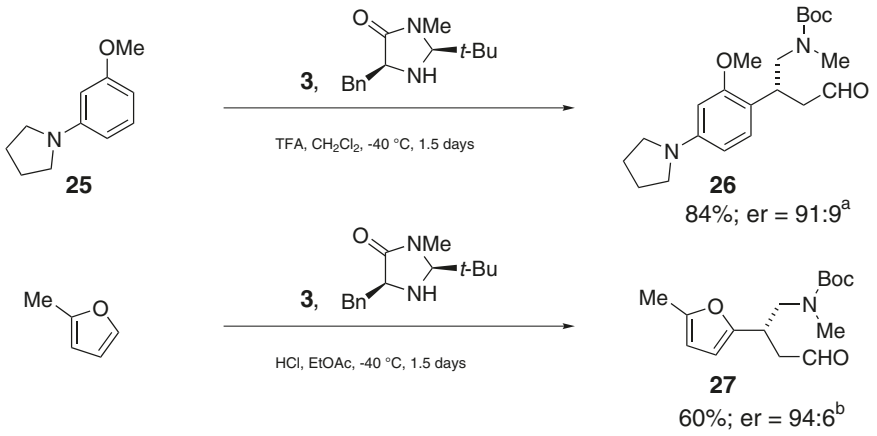
Scheme 4. Synthesis of naratriptan analogs. Reagents and conditions: (*a*) (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one, TFA, *i*-PrOH, CH_2Cl_2, –70 °C, 1 day; (*b*) TsOH–H_2O, MeOH, 70% (two steps); (*c*) H_2 (8 atm; 1 atm = 101.325 kPa), Rh-C, AcOH, 62% or BF_3–OEt_2, Et_3SiH, 58%; (*d*) BF_3–OEt_2, allyltrimethylsilane, 23%.



Scheme 5. The use of bis-protected aldehyde **15** to generate a substrate suitable for indole-3-pyrrolidine synthesis. Reagents and conditions: (*a*) **15**, (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one, TFA, *i*-PrOH, CH_2Cl_2, –70 °C, 1.5 day; (*b*) $NaBH_4$, MeOH, 84%; (*c*) (*i*) MsCl, TEA, 70%; (*ii*) HCl, EtOAc; (*iii*) K_2CO_3, DMF, 85%; (*d*) (*i*) α-chloroethylchloroformate, CH_2Cl_2; (*ii*) MeOH, reflux, 45%.



Scheme 6. Synthesis of enantioenriched phenethylamines and 2-ethylamino furans.



To circumvent the acid-induced decomposition of aldehyde **16a** to *N*-Boc–pyrrole, we investigated an alternative approach (Scheme 5) now utilizing the enantiomeric MacMillan catalyst *ent*-(–)-(**2**).

Starting from **21** (Table 1, entry 5), we first reduced the aldehyde to the primary alcohol **22**. Mesylation of alcohol **22** and removal of the Boc group resulted in a spontaneous cyclization to the pyrrolidine **23**. Removal of the PMB protecting group was easily accomplished using α-chloroethylchloroformate[14] to furnish **24**, the des-*N*-methyl enantiomer of *S*-(–)-**1**.

Paras and MacMillan[7e] reported Friedel–Crafts type conjugate additions of electron-rich aromatics and heterocyclics to α,β-unsaturated aldehydes. The extension of this reaction to 4-*N*-Boc-*N*-methyl butanal provided access to enantioenriched 3-substituted butanals. Thus, the treatment of **3** with 3-pyrrolidino anisole in the presence of the MacMillan (*S*,*S*) imidazolinone catalyst *ent*-**2** in methylene chloride at –40 °C led to the phenethylamine derivative **26** in an 84% yield and 91:9 enantiomeric ratio (Scheme 6). A similar reaction with 2-methylfuran, albeit using EtOAc as the solvent, led to the substituted 2-methylfuran derivative **27** in a 60% yield and 94:6 enantiomeric ratio.

Conclusion

Butanals containing N substituents at the γ-carbon atom are excellent substrates for Michael and Friedel–Crafts type conjugate additions of indoles and electron-rich aromatics,

respectively, affording suitably functionalized adducts in high diastereomeric ratios. The extension of MacMillan's organocatalytic indole alkylation to nitrogen-containing aldehydes was realized and has found application in our concise synthesis of *S*-(–)-**1**, a late-stage intermediate in the synthesis of the dual action migraine drug prototype NXN274. We expect that this methodology will also find applications in alkaloid synthesis and in the synthesis of other indole-containing compounds of medicinal interest.

Experimental

General

The *J* values are spacings measured directly from the spectrum. Dry solvents were purified using a sodium dodecyl sulfate (SDS) system or purchased as such (Sigma-Aldrich). Column sizes are quoted as (width × height). Melting points were measured on a Büchi melting point B-540 apparatus and are uncorrected. Optical rotations were recorded on a PerkinElmer model 343 polarimeter at ambient temperature.

N-*Allyl*-N-*4-methoxybenzylamine (12)*

Anisaldehyde (0.44 mL, 3.6 mmol), allylamine (0.29 mL, 1.1 equiv), and $MgSO_4$ (0.5 g) in CH_2Cl_2 (5.4 mL) were mixed and the solution was stirred for 3 h (TLC control) and then the mixture was filtered and the filtrate solution was concentrated in vacuo.[15]

The crude aldimine was then taken up in MeOH (6 mL) and 4 Å molecular sieves (1 g), followed by $NaBH_4$ (0.13 g, 3.4 mmol) were added with stirring. The flask was flushed with Ar and stirring was continued for 2 h, then the mixture was diluted with Et_2O (25 mL) and extracted twice with 10% HCl (10 mL each). The combined acidic extracts were basified with 3 N NaOH and extracted twice with Et_2O (30 mL total). The combined ethereal extracts were dried (Na_2SO_4) and evaporated to afford **12** (0.34 g, 54%), which had data identical to that previously reported.[15]

N-tert-*Butylcarbonyl*-N-*allyl*-N-*4-methoxybenzylamine (13)*

Boc_2O (0.49 mL, 1.1 equiv) was added to a stirred solution of **12** (0.3421 g, 1.930 mmol) in THF (6 mL) under Ar and the mixture was stirred at rt overnight. Removal of the volatiles in vacuo afforded **13** (0.4865 g, 91%), having spectral data identical to that previously reported.[16]

*4-[*tert-*Butoxycarbonyl-(4-methoxy-benzyl)amino]but-2-enoic acid methyl ester (14)*

The Grubbs II catalyst (34 mg, 0.040 mmol) was added to a stirred solution of **13** (0.4159 g, 1.500 mmol) and methyl acrylate (5.4 mL) in CH_2Cl_2 (6.6 mL). The flask was flushed with Ar and stirring was continued overnight. The mixture was filtered through a plug of SiO_2 (2 cm × 2 cm) using 5% EtOAc–hexanes to wash the plug and then the volatiles were removed in vacuo. Flash chromatography over SiO_2 (1.5 cm × 25 cm) using 5% EtOAc–hexanes afforded **14** (0.2594 g, 52%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (br s, 2H), 6.85 (d, J = 8.44 Hz, 2H), 6.82–6.86 (m overlapping with previous, 1H), 5.81–5.85 (m, 1H), 4.36 (br s, 2H), 3.94 (br s, 1H), 3.79 (s, 3H), 7.74–3.80 (m overlapping, 1H), 3.74 (s, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.4, 46.6, 49.2, 51.6, 55.3, 80.3, 114.0, 121.6, 128.8, 129.3, 129.6, 144.1, 155.4, 159.0, 166.5 (peaks at 128.8 and 129.3 appear to arise from a single C, but doubled owing to Boc carbamate). Exact mass *m/z* calcd for $C_{18}H_{25}NNaO_5$: 358.16249 (M + Na); found: 358.16086.

(4-Methoxy-benzyl)-(4-oxo-but-2-enyl)carbamic acid tert-*butyl ester (15)*

DIBAL-H (1.6 mL, 1 mol/L in hexanes, 1.6 mmol) was added via syringe to a stirred and cooled (–78 °C) solution of **14** (0.2426 g, 0.7432 mmol) in PhMe (2.2 mL) under Ar. After 30 min, the cooling bath was removed and the mixture was quenched by the addition of saturated aqueous Rochelle's salt (1.5 mL), diluted with Et_2O (20 mL), and washed once with saturated aqueous Rochelle's salt (5 mL). The organic layer was allowed to stand overnight and the next day the gel that formed was filtered through Celite. Filtration of the residue through a pad of SiO_2 (2 cm × 2 cm) using 40% EtOAc–hexanes afforded the allylic alcohol (0.1152 g, 52%), which was oxidized using the Parikh–Doering method.

SO_3–pyridine (0.12 g, 0.75 mmol) was added in one portion to a stirred and cooled (0 °C) solution of allylic alcohol (from the DIBAL reduction; 0.1152 g, 0.3748 mmol), Et_3N (0.10 mmol), and DMSO (0.22 mL) in CH_2Cl_2 (3 mL). Stirring was continued for 10 min before the ice bath was removed and stirring was then continued for a further 2 h. The mixture was then diluted with CH_2Cl_2 (5 mL) and the mixture was washed once with water (6 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over SiO_2 (1.5 cm × 20 cm) using 20% EtOAc–hexanes afforded **15** (85.1 mg, 74%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (d, J = 7.8 Hz, 1H), 7.14 (br s, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.67 (br s, 1H), 6.08 (dd, J = 7.4, 15.4 Hz, 1H), 4.36 (br s, 2H), 3.97–4.05 (m, 2H), 3.79 (s, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.4, 47.1, 49.7 and 50.1 (doubled peak), 55.3, 80.6, 114.0, 128.8, 129.5, 132.5, 152.9, 155.3, 159.1, 193.2. Exact mass *m/z* calcd for $C_{17}H_{23}NNaO_4$: 328.15193 (M + Na); found: 328.15163.

*4-(5-Bromo-1*H-*indol-3-yl)-3,4-dihydro-2*H-*pyridine-1-carboxylic acid* tert-*butyl ester (17)*

A flask was charged with MacMillan's catalyst (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidaolidin-4-one (6.8 mg, 0.13 mmol) and then TFA (0.04 mL, 0.03 mmol) was introduced via syringe. The flask was flushed with Ar, cooled to –70 °C (cooling machine), and **16b** (0.4012 g, 2.014 mmol) in CH_2Cl_2 (1.3 mL) and *i*-PrOH (0.2 mL) were introduced via syringe. The mixture was stirred for 5 min, then 5-bromoindole (0.13 g, 0.67 mmol) was added in one portion. The flask was reflushed with Ar and stirring was continued for 1.5 days, at which point condensing atmospheric water had caused the acetone cooling bath to reach –65 °C. The mixture was removed from the cooling bath, diluted with CH_2Cl_2 (10 mL), washed once with water, and dried ($MgSO_4$). Flash chromatography of the residue over SiO_2 (1.5 cm × 20 cm) using 25% EtOAc–hexanes afforded **17** (66 mg), which was converted directly to **18** (see the following section). An analytical sample had $[\alpha]_D^{25}$ +14.6° (*c* 0.77, $CHCl_3$). FT-IR (film cast, cm^{-1}): 3431, 1678, 1648, 1458, 1406, 1367, 1299, 1235, 1164, 1120, 987. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (br s, 1H), 7.76 (s, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.24 (dd, J = 8.2, 0.4 Hz, 1H), 6.91–7.07 (m, 1H), 6.97 (d, J = 2.1 Hz, 1H), 4.97–5.09 (m, 1H), 3.66–3.73 (overlapping m, 2H), 3.42–3.50

(m, 1H), 2.18 and 1.96 (two br s, 1H), 1.61 and 1.50 (two s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.2, 28.6, 28.9, 39.0, 40.0, 80.7, 107.1, 107.5, 112.4, 112.5, 119.4, 121.3, 123.0, 123.3, 124.8, 125.5, 125.8, 127.8, 128.2, 135.1, 152.1, 152.7. Exact mass *m/z* calcd for $C_{18}H_{21}BrN_2NaO_2$: 399.06786 (M + Na); found: 399.06807.

4-(5-Bromo-1*H*-indol-3-yl)-2-methoxypiperidine-1-carboxylic acid* tert-*butyl ester (18)

$TsOH–H_2O$ (2 mg, 0.01 mmol) was added to a stirred solution of **17** (66 mg, assumed to be 0.67 mmol from the previous transformation) in MeOH (2 mL). The flask was flushed with Ar and stirring was continued for 1 day. Evaporation of the solvent and flash chromatography over SiO_2 (1.5 cm × 20 cm) using 20% EtOAc–hexanes afforded **18** as a mixture of diasteromers (39.4 mg, 72%).

4-(5-Bromo-1*H*-indol-3-yl)-piperidine-1-carboxylic acid* tert-*butyl ester (19)

Et_3SiH (0.3 mL, 5% v/v in CH_2Cl_2, 0.1 mmol) followed by BF_3-OEt_2 (0.14 mL, 5% v/v in CH_2Cl_2, 0.057 mmol) were added via syringe to a stirred and cooled (–78 °C) solution of **18** (9.7 mg, 0.024 mmol) in CH_2Cl_2 (0.5 mL) under Ar. The mixture was stirred for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL). The aqueous phase was extracted once with CH_2Cl_2 (5 mL) and dried ($MgSO_4$). Flash chromatography over SiO_2 (0.5 cm × 10 cm) using 20% EtOAc–hexanes afforded **19** (5.2 mg, 58%); mp 199–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (br s, 1H), 7.72 (m, 1H), 7.19–7.26 (overlapping m, 2H), 6.93–6.94 (m, 1H), 4.21 (ddd, *J* = 13.3, 2.1, 2.1 Hz, 2H), 2.84–2.95 (m overlapping with next, 1H), 2.85 (ddd, *J* = 13.0, 13.0, 2.4 Hz, 1H), 2.02–1.96 (m, 2H), 1.54–1.67 (m, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.4, 22.0, 39.4, 123.9, 126.4, 127.0, 128.1, 128.2, 129.3, 142.1, 143.9, 155.5 (signals from Boc *t*-Bu did not appear). Exact mass *m/z* calcd for $C_{18}H_{23}BrN_2NaO_2$: 401.08351 (M + Na); found: 401.08548. X-ray crystallographic data are given in Appendix 1 in the Supplementary data. Compounds **18** and **19** had the same R_f by TLC; however, **19** stained purple with anisaldehyde.

(R)-2-Allyl-(5-bromo-1*H*-indol-3-yl)piperidine-1-carboxylic acid* tert-*butyl ester (20)

Allyltrimethylsilane (0.02 mL, 0.13 mmol) followed by BF_3-OEt_2 (0.22 mL, 5% v/v in CH_2Cl_2, 0.089 mmol) were added via syringe to a stirred and cooled (–78 °C) solution of **18** (16.1 mg, 0.039 mmol) in CH_2Cl_2 (0.5 mL) under Ar. The mixture was stirred for 1 h, then quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL). The aqueous phase was extracted once with CH_2Cl_2 (5 mL) and dried ($MgSO_4$). Flash chromatography over SiO_2 (0.5 cm × 10 cm) using 20% EtOAc–hexanes afforded **20** (3.7 mg, 23%). Compounds **18** and **20** had the same R_f by TLC; however, **20** stained a different colour using anisaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (br s, 1H), 7.71 (m, 1H), 7.19–7.27 (overlapping m, 2H), 6.92–6.93 (m, 1H), 5.79 (dddd, *J* = 17.1, 10.1, 7.2, 7.2 Hz, 1H), 5.12 (dddd, *J* = 18.4, 1.9, 1.9, 1.9 Hz), 5.05–5.09 (m, 1H), 4.42 (app br s, 1H), 4.13 (app br s, 1H), 2.95–3.20 (m, 1H), 2.36–2.58 (m, 1H), 1.71 (ddd, *J* = 13.3, 13.3, 5.5 Hz, 1H), 1.41–1.50 (overlapping m, 2H), 1.46 (s, 9H), 0.81–0.95 (m, 1H). Exact mass *m/z* calcd for $C_{21}H_{27}BrN_2NaO_2$: 441.11481 (M + Na); found: 441.11557.

Supplementary data

Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0221. CCDC 898223 contains the X-ray data in CIF format for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/products/csd/request. (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 33603; or e-mail: deposit@ccdc.cam.ac.uk.)

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Fonds de Recherche du Québec (FQRNT) for financial assistance and Benoît Deschênes-Simard (Hanessian group) for X-ray structure determination.

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Studies of neodolastanes — Synthesis of the tricyclic core of the trichoaurantianolides

David R. Williams and Joseph R. Pinchman

Abstract: Studies toward the synthesis of trichoaurantianolide C (**5**) are described. Stille cross-coupling reactions of (*E*)- and (*Z*)-β-stannyl-α,β-unsaturated esters with allylic acetate **32** provide for the stereocontrolled formation of nonconjugated 2,5-diene-1-ols. Studies of the asymmetric Sharpless epoxidation are utilized to establish diastereofacial selectivity for the preparation of a crucial C_2 tertiary allylic alcohol for subsequent esterification and ring-closing metathesis. SmI_2 reductive cyclization of the key butenolide precursor **49** led to formation of the central seven-membered ring of the tricyclic core of the natural product.

Key words: π-allyl Stille cross-coupling, reductive cyclization, stereoselective synthesis.

Résumé : On décrit une série d'études réalisées dans le but de faire la synthèse du trichoaurantianolide C (**5**). Des réactions de couplages croisés de Stille entre des esters (*E*)- et (*Z*)-β-stannyl-α,β-insaturés et l'acétate allylique **32** conduisent à la formation stéréocontrôlée de 2,5-dién-1-ols non conjugués. On a utilisé les méthodes d'époxydation asymétrique de Sharpless pour déterminer la sélectivité diastéréofaciale pour la préparation d'un alcool allylique tertiaire en C_2 crucial pour l'estérification subséquente et la réaction de métathèse qui permet d'effectuer la fermeture du cycle. La cyclisation réductrice à l'aide de SmI_2 du précurseur buténolide clé **49** conduit cycle central à sept chaînons de la partie tricyclique fondamentale du produit naturel.

Mots-clés : couplage croisé π-allylique de Stille, cyclisation réductrice, synthèse stéréosélective.

[Traduit par la Rédaction]

Introduction

Natural products of the dolabellane and dolastane families have been studied as significant targets for synthesis because they present a number of interesting structural features as well as an impressive array of biological activities.[1] These metabolites share a common biogenetic pathway from geranylgeranyl pyrophosphate via the dolabellane cation **1** (Fig. 1), which may give rise to 3,7-dolabelladienes (**2**) by elimination or capture by water. In 1976, Ireland et al.[2] first described the isolation of the dolabellanes as secondary metabolites of the sea hare *Dolabella californica*, and the first synthesis was described in 1993.[3,4] Since these initial reports, approximately 150 examples have been discovered from marine and terrestrial sources.[5] A stereospecific backbone migration of substituents in the dolabellane cation **1** results in the neodolabellanes, as exemplified by β-neodolabellenol (**3**).[6] The neodolabellanes have been exclusively found in various species of coral. On the other hand, it is apparent that the dolabellanes and many related derivatives are available in the biosphere as examples of the *d*- or *l*-enantiomeric series based on an initial species-specific cyclization. This can be a challenging issue for natural product isolation because of problems resulting from the seawater filtration of feeding organisms, cohabitation, and symbiotic fungi. The [9.3.0] cyclotetradecane framework of **2** and **3** may also give rise to interesting transannular events.[7] In fact, the 3,7-dolabelladienes are key precursors to the dolastanes,[8] a class of 5–7–6 tricyclic marine terpenes, as illustrated in dolatriol (**4**), as well as the fusicoccanes of fungi origin that feature the 5–8–5 carbocyclic skeleton.[9] Similarly, the initiation of a transannular reaction in the neodolabellene series (**3**) yields the corresponding family of neodolastanes, and the first examples of these diterpenes were independently discovered by Vidari and co-workers[10] and Steglich and co-workers.[11] Thus, trichoaurantianolides A–D (trichoaurantianolide C (**5**)) were isolated from a *Tricholoma* species, a large genus of gilled mushrooms. In these structures, the anticipated 5–7–6 tricyclic neodolastane core is otherwise disguised by subsequent oxidations of the cyclohexenyl ring, which is reorganized with the fusion of a butyrolactone and the unsaturated tetrahydrofuranyl system featured in **5**. Extensive NMR studies have established the relative stereochemistry and structural connectivity of the trichoaurantianolides, and Steglich and co-workers[11] assigned the absolute configuration of trichoaurantianolide B by X-ray crystallographic analysis. Subsequently, Sterner and co-workers[12] reported the isolation of lepistol (**6**) and its corresponding aldehyde, which are deoxygenated C_8 derivatives of **5**. In 2003, Ohta and co-workers[13] further described the characterization of tricholomalides A, B, and C (tricholomalide A, **7**), and these studies concluded that the absolute configuration

Received 22 June 2012. Accepted 1 September 2012. Published at www.nrcresearchpress.com/cjc on 20 December 2012.

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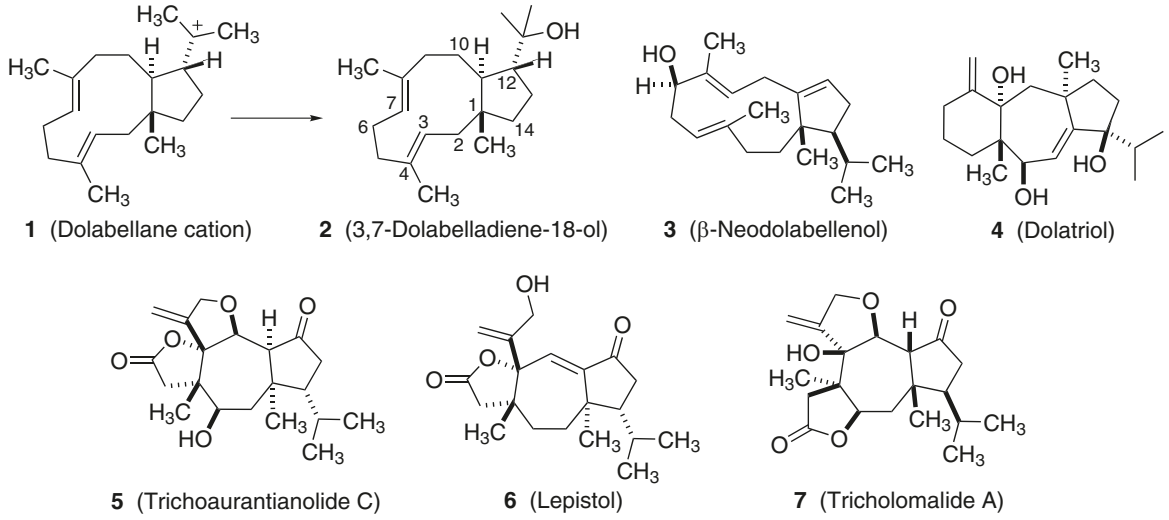
This article is part of a Special Issue dedicated to Professor Derrick Clive in celebration of his many contributions to organic chemistry.

Fig. 1. Representative dolabellane and dolastane diterpenes.



is opposite to that assigned for the trichoaurantianolides based on studies of circular dichromism. In 2009, Danishefsky and coworkers[14] reported a structure revision and total synthesis for racemic tricholomalides A and B. In addition, examples of the guanacastepene family have subsequently characterized these diterpenes as 5–7–6 representatives of the neodolastane family. The guanacastepenes have been the subject of a number of synthesis studies.[15]

Results and discussion

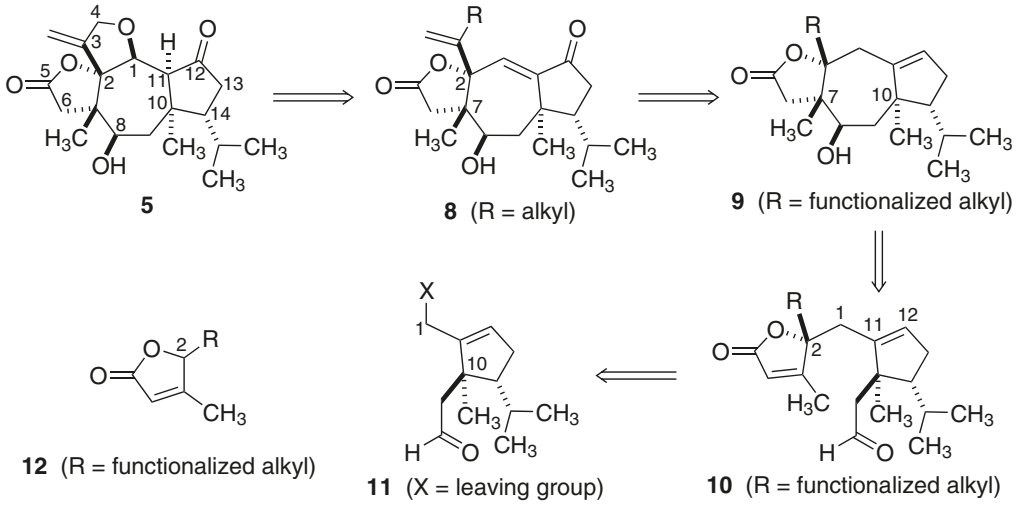
Trichoaurantianolide C (**5**) exhibits a novel neodolastane skeleton in which the cyclohexane precursor of these metabolites is oxidatively cleaved and transformed into the cis-fused lactone and a bridging tetrahydrofuran containing C_2, C_3, and C_4 of the original carbocycle. We sought to address the challenging aspects presented by seven contiguous stereogenic carbon centers in **5** with a retrosynthetic plan (Scheme 1) designed to simplify the required tasks. We have focused our attention on the tricyclic lactone **9** as a key intermediate, which displays the trans orientation of methyl substituents at C_7 and C_{10}. This rationale suggests that a reductive cyclization of the butenolide **10** would achieve our objective via the diastereoselective formation of the seven-membered ring. In principle, our goal for an enantiocontrolled synthesis would be met by a convergent approach that provides a stereocontrolled alkylation of a suitably rendered nonracemic cyclopentene **11** with the substituted butenolide **12**. Indeed, the latter disconnection is seen as a critical barrier for success of the overall plan because of the need to establish the appropriate chirality at C_2 of **10**. To circumvent this problem, our studies have explored two strategies to satisfy this stereochemical requirement. Firstly, the C_2 chirality may be directly incorporated into **10** by an alkylation leading to C_1–C_{11} bond formation. This approach would mask the butenolide of **12** as an enantiopure synthon that contains an additional carbon (C_1) as well as the desired C_2 stereochemistry. Alternatively, we have reasoned that the allylic C_1–C_2 bond of **10** could readily be formed if this operation were to precede installation of the C_2 chirality. The latter alternative suggests a reagent-controlled reaction for accessing the desired C_2 configuration in the butenolide **10**.

The preparation of the enantioenriched cyclopentene precursors is summarized in Scheme 2. We have previously described the synthesis of racemic cyclopentenone **13** beginning with 2-methyl-2-cyclopenten-1-one via cuprate conjugate addition, enolate alkylation with allyl bromide, and oxidative cleavage followed by selective reduction.[16] The Corey–Bakshi–Shibata (CBS) reduction[17] of ketone **13** has been used to effect a resolution by generating equal amounts of the diastereomeric alcohols **14** and **15** (diastereomeric ratio (dr) 1:1). The diastereomers are readily separated by flash chromatography on a multigram scale, and the oxidation of alcohol **14** provided the nonracemic ketone (–)-**13** ($[\alpha]_D^{20}$ –57.6 (*c* 2.04, $CHCl_3$)) for further chemistry. Hydrazone formation is followed by radical decomposition of **16** with iodine in the presence of tetramethylguanidine (TMG) to yield the alkenyl iodide **17**,[18] and halogen–metal exchange readily produced high yields of ethyl ester **18** for reduction to the nonracemic allylic alcohol **19**.

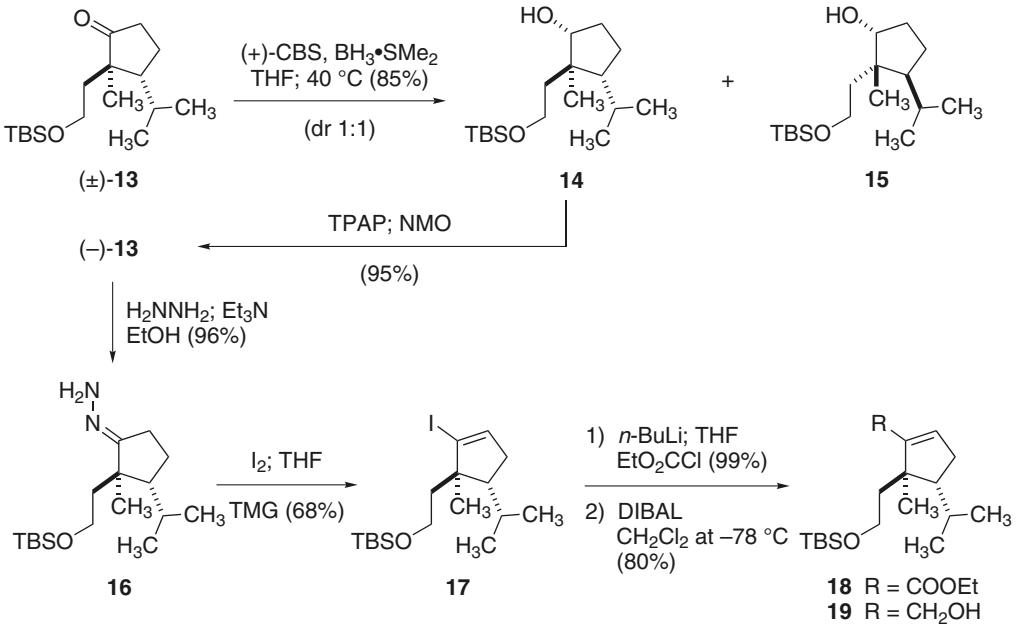
With ample quantities of the cyclopentene components in hand, our studies examined a strategy for formation of the C_1–C_{11} bond of the intermediate lactone **20** (Fig. 2). We rationalized that a direct alkylation by nucleophilic displacement of the hindered unreactive bromide of **21** would be problematic. This difficulty may be overcome by the reaction of the epoxide **22** with an appropriate alkenylmetal species (**23**) to yield the desired **20** via facile lactonization. However, plans for the straightforward preparation of nonracemic **21** or **22** were not apparent. This concept can be extended to the racemic six-membered lactone **24**, which may be prepared with excellent enantioselectivity. Nucleophilic opening of the terminal oxirane of **24** and internal transesterification would produce lactone **20**.

To test this idea, initial efforts provided the racemic epoxide **24** in three steps from the known keto-alcohol **25**[19] via nucleophilic epoxidation and esterification to yield the ketophosphonate **26** for ring closure by an internal Horner–Wadsworth–Emmons olefination using the LiCl/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) protocol.[20] However, our subsequent experiments leading to the formation of a higher order cuprate from the alkenyl iodide **17** proved to be capricious. In these efforts, the novel triene **28** was characterized as the product of S_N2' opening

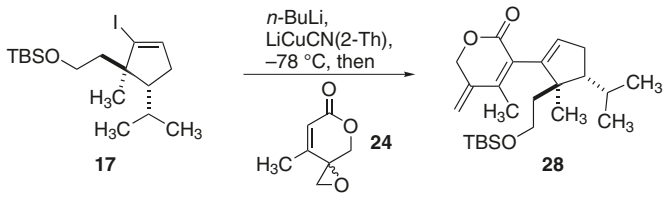
Scheme 1. Retrosynthetic analysis.



Scheme 2. Preparation of enantioenriched cyclopentenes.

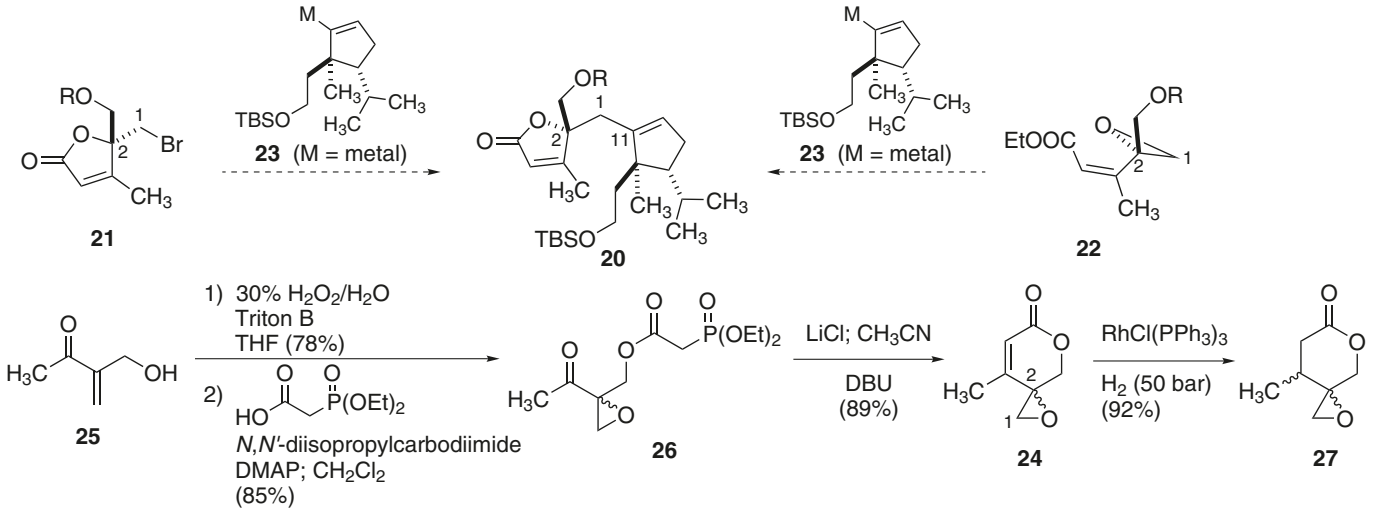


of the epoxide **24** (15%–20% yields). The reduced alkene of **17** and unreacted enone **24** were substantially recovered. To circumvent this issue, the saturated lactone **27** was also prepared by hydrogenation with Wilkinson's catalyst at elevated hydrogen pressure (50 bar; 1 bar = 100 kPa). Unfortunately, the terminal epoxide **27** proved to be completely unreactive with various cuprates derived from the metalation of iodide **17**.

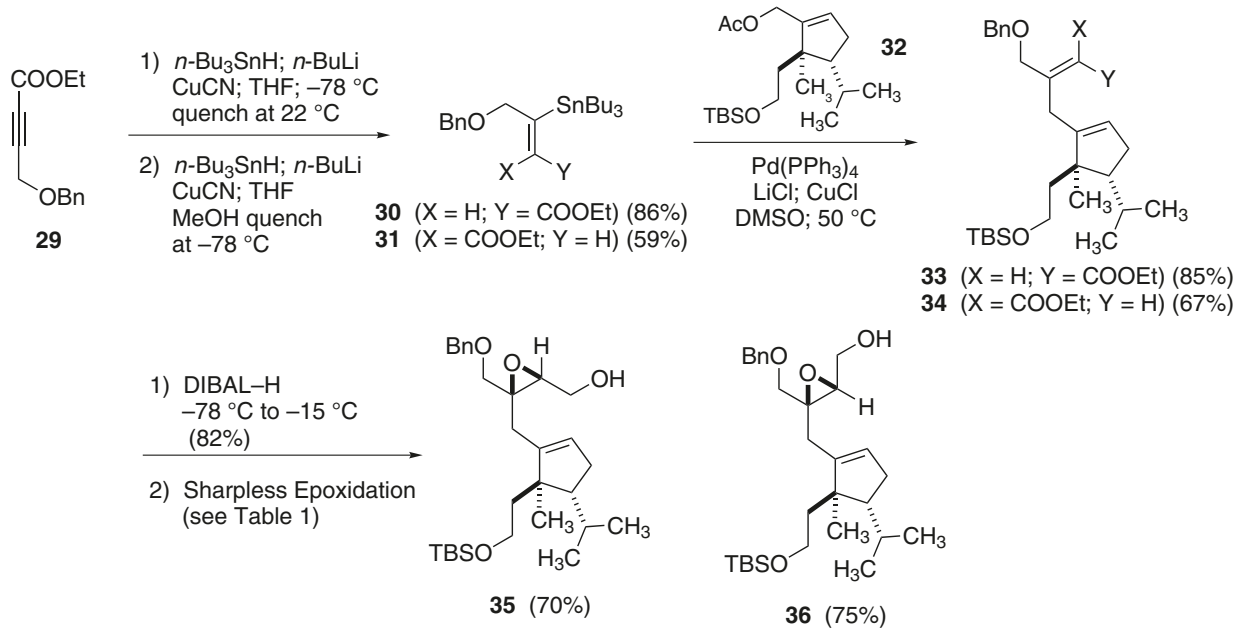


Concomitantly, our plans for C_1–C_2 bond formation began to show promise for subsequent introduction of C_2 chirality in **20**. As summarized in Scheme 3, the conjugate addition of tri-*n*-butylstannyl cuprate with alkynyl ethyl ester **29** affords the (*Z*)-α,β-unsaturated product **30** in an excellent yield with high stereoselectivity when these reactions are quenched after warming to 22 °C. On the other hand, the (*E*)-product **31**, resulting from syn addition of the cuprate reagent, is obtained by the inclusion of anhydrous methanol for a kinetic quench at –78 °C.[21] In this fashion, the individual *Z*- and *E*-isomers **30** and **31**, respectively, have been examined in studies of π-allyl Stille cross-coupling reactions[15h,22] with the allylic acetate **32**, which is available from the nonracemic alcohol **19** (Scheme 2). Gratifyingly, the Stille cross-coupling processes demonstrated

Fig. 2. Initial considerations for C_1–C_{11} bond formation in **20**.



Scheme 3. Preparation of (*E*)- and (*Z*)-epoxy alcohols.



high stereocontrol in both cases and provided good yields of the individual isomers, (*E*)-**33** (85%) and (*Z*)-**34** (67%). Our plan to establish C_2 chirality by means of a chemoselective asymmetric epoxidation is facilitated by the convenient reduction of **33** and **34** to their corresponding (*E*)- and (*Z*)-allylic alcohols. Indeed, a site selective oxidation of the nonconjugated 2,5-diene-1-ols was readily achieved under the conditions of the asymmetric Sharpless epoxidation with *tert*-butyl hydroperoxide.[23] However, surprisingly poor diastereofacial selectivity was observed for epoxidations for the (*E*)-allylic alcohol leading to **35** (Table 1, entries 1–4). A change to (+)-diisopropyl-L-tartrate (L-DIPT) and a decrease in catalyst loading offered minimal improvements favoring **35** (dr 65:35; Table 1, entry 4). The absence of a clear facial preference and the inability to separate the diastereomeric products also prevents a confident assignment of stereochemistry at this point. By comparison, the corresponding (*Z*)-allylic alcohol produced a selective epoxidation to yield **36** (dr 92:8; Table 1, entry 5) using D-DIPT.

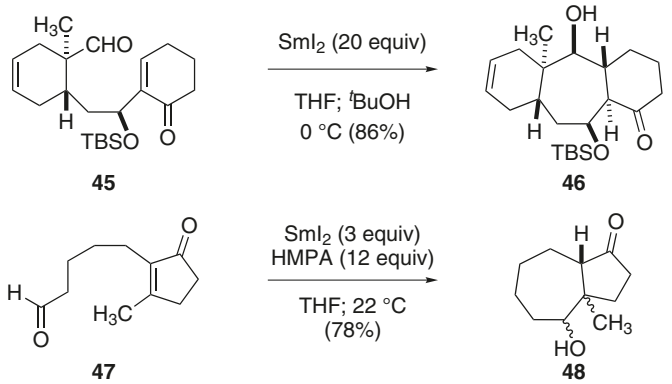
The assignments of epoxide stereochemistry in these experiments are clarified by subsequent transformations leading to the tricyclic core of trichoaurantianolide C. Progress toward this goal independently utilized inseparable oxiranes (Table 1, entries 3 and 5) for the reaction sequence

Table 1. Conditions for asymmetric Sharpless epoxidation.

Entry	Allylic alcohol	Tartrate (equiv)	Ti(O-*i*-Pr)$_4$ (equiv)	Epoxide (dr)
1	(*E*)	L-DET (1.6)	0.6	45:55
2	(*E*)	L-DET (0.26)	0.2	55:45
3	(*E*)	L-DIPT (1.3)	1.0	60:40
4	(*E*)	L-DIPT (0.12)	0.1	65:35
5	(*Z*)	D-DIPT (0.6)	0.5	92:8

illustrated in Scheme 4 to yield the desired butenolides. Thus, the conversion to the epoxy bromides **37** is followed by the addition of *n*-butyllithium at low temperature to give a mixture of C_2 tertiary alcohols, **38**. Acylation of the hindered alkoxide with freshly distilled acryloyl chloride affords esters **39** (70% yield, 81% based on recovered starting material (brsm)), and this material is immediately submitted for ring-closing metathesis (RCM).[24] A survey of RCM catalysts and conditions revealed that the Grubbs II catalyst[25] is extremely effective and provides nearly quantitative yields of the five-membered lactone **40**. To install the remaining methyl substituent at C_7, we utilized a two-step procedure for facile conjugate addition with dimethylcuprate in ether at –25 °C (86%) followed by α-selenation of the enolate and oxidative elimination using metachloroperbenzoic acid. After deprotection, the diastereomers **43** and **44** were successfully separated and fully characterized. Butenolide **43** was characterized as the major product stemming from the asymmetric Sharpless epoxidation, and this substance was advanced for our studies of reductive cyclization.

Our efforts for the formation of the central seven-membered ring of trichoaurantianolide C focused on the use of samarium diiodide, which has been widely utilized for intramolecular reductive ketyl-enone/enoate coupling reactions of five- and six-membered systems.[26,27] There are relatively few studies that feature intramolecular reductive coupling reactions to yield seven- and eight-membered examples. In this regard, Arimotoand co-workers[28] described high stereoselectivity for the reductive cyclization of **45** to give the tricyclic ketone **46**.[29] However, Tori and co-workers[30] reported approximately equal amounts of all four diastereomers of **48** in the SmI_2 reduction of the unrestricted enone **47**.

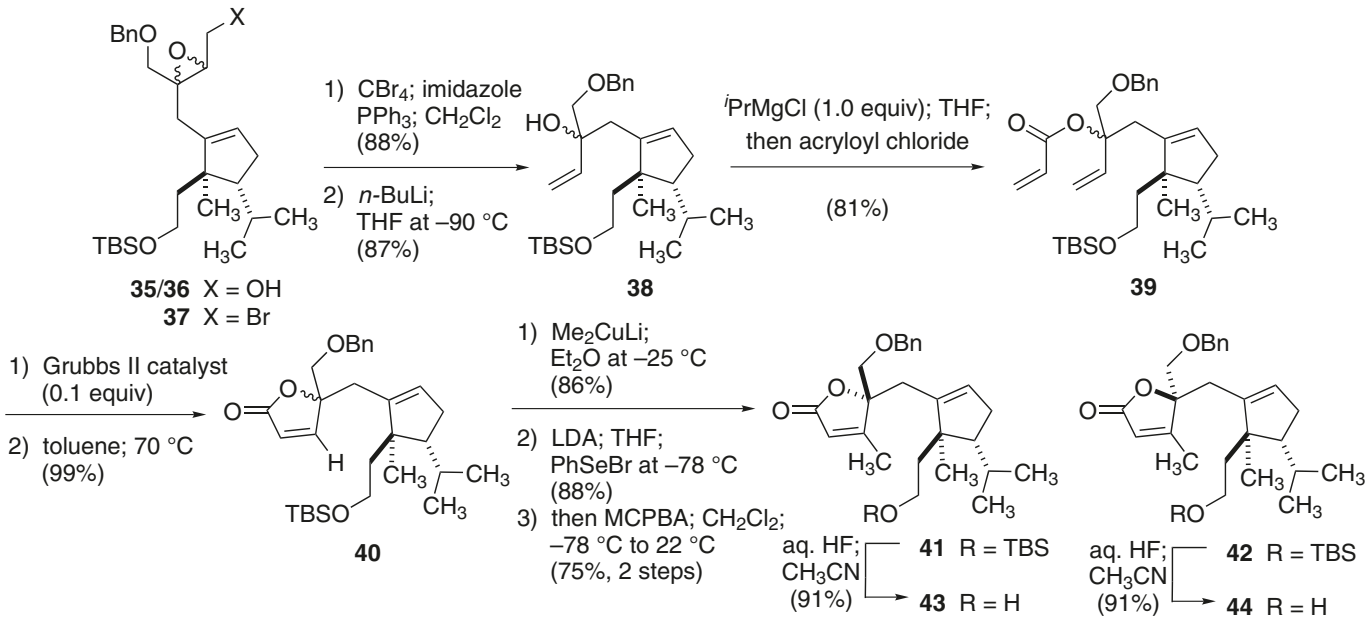


A number of variables are key factors that can affect the outcome of these SmI_2 cyclizations, including the geometry of the substrate, the influence of a proton source, and the presence of certain additives. For example, methanol forms a complex with SmI_2, whereas *tert*-butyl alcohol does not lead to complexation.[31] Procter and co-workers[32] found that changing the proton source from methanol to *tert*-butyl alcohol may produce different cyclization pathways. Inorganic salts, such as LiCl and NiI_2, and cosolvents, including hexamethylphosphoramide (HMPA), *N*-methyl-2-pyrrolidinone (NMP), and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), have effectively increased the oxidation potential of the reduction.[33,34]

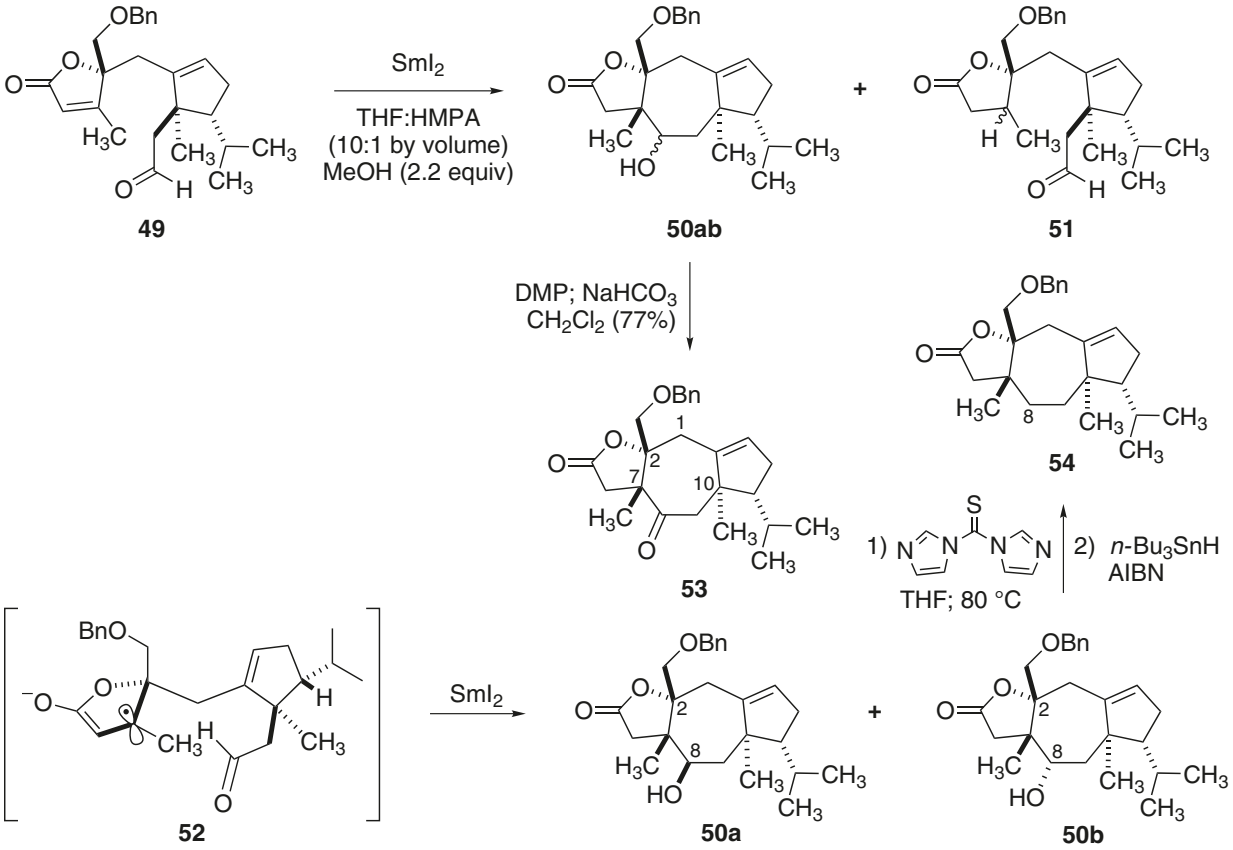
As summarized in Scheme 5, aldehyde **49** is readily prepared from alcohol **43** (Dess–Martin periodinane, CH_2Cl_2, 92% yield). However, the initial attempts for SmI_2 cyclizations in dry tetrahydrofuran (THF) containing methanol (2.2 equiv led only to recovered starting material. When HMPA is included as a cosolvent (THF/HMPA, 10:1 by volume), significant amounts of the desired products **50a** and **50b** (dr 85:15) are obtained (30% yield), accompanied by an equal quantity of the uncyclized reduced butyrolactone **51** as a mixture of diastereomers.

We were somewhat surprised that the aldehyde had survived these conditions, and subsequently we investigated SmI_2 reductions in the absence of a proton source. At 0 °C, an excess of SmI_2 (6 equiv) is required for consumption of the starting material, and a rapid conversion to the desired **50a** and **50b** is apparent by thin-layer chromatography (TLC). However, various quenching procedures lead to a crude mixture that contains substantial amounts of side products. These experiments produced approximately 50% yields of the desired cycloheptanes **50a** and **50b** (dr 1:1) after careful chromatography. When *tert*-butyl alcohol is introduced as a proton source, in addition to the use of HMPA, these reactions produce fewer side products and the yield of the reductive cyclization is increased to 63% with a modest preference for the formation of β-alcohol **50a** (dr 65:35). The desired reaction proceeds via the initial formation of the ketyl radical **52**, arising from a one-electron reduction of the α,β-unsaturated lactone. Introduction of a second electron at the aldehyde site may lead to a diradical species for C–C bond formation by radical cyclization. Alternatively, further reduction of **52** would produce a dianion as a two-electron reduction, which could account for competing cyclization to provide the diastereomeric alcohols **50a** and **50b** or protonation to give the byproduct **51**. The tethered arrangement of **52** provides an energetically favored conformational bias for facial selectivity. Thus, the arrangement of 7,10-*anti*-dimethyl substituents in the products **50a** and **50b** is enforced by the substantial steric requirements leading to the cis-fused butyrolactones. The diastereomers were separated and characterized with 2D NMR spectroscopic analysis. Significantly, the 2D-NOESY analysis identifies key correlations between the C_7 methyl and C_2 methylene substituents (refers to natural product numbering; see Scheme 1) to support the assignment of the cis-fused lactone. The stereochemistry of the C_8 alcohol is established by 2D NOESY correlations between the C_8 hydrogen and the C_{10} methyl as well as the α-hydrogen at C_1. The minor isomer **50b** shows the expected correlations of the β hydrogen at C_8 with the C_2 and C_7 alkyl groups. Oxidation of a mixture of these diastereomers yielded ketone **53** as a crystalline solid, and X-ray crystallographic studies unambiguously confirmed the stereochemistry of the tricyclic system (Fig. 3).[35] This

Scheme 4. Formation of butyrolactones **43** and **44**.

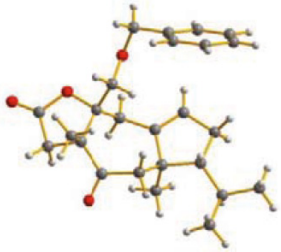


Scheme 5. Formation of the tricyclic core of trichoaurantianolide D.

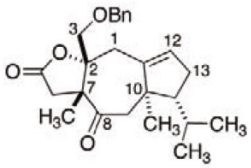


result also confirms the absolute stereochemistry of the major lactone diastereoisomer **50a** as the desired C_2 configuration, which is produced in the Sharpless epoxidation affording epoxy alcohol **36** (dr 92:8). The parent ring system conserved within this family of neodolastanes also was characterized by Barton–McCombie deoxygenation of alcohol **50b**, yielding the tricyclic lactone **54** as featured in lepistol and related natural products.

Fig. 3. ORTEP of ketone **53**.



ORTEP of Ketone **53**



53 (Trichoaurantianolide numbering)

Conclusions

In summary, we have devised an enantioselective pathway for the synthesis of neodolastane metabolites as exemplified by trichoaurantianolide C. Our studies have described an efficient π-allyl Stille cross-coupling reaction, and we have resolved some unanticipated problems stemming from the asymmetric Sharpless epoxidations of our nonracemic *E*- and *Z*-2,5-diene-1-ols. Samarium-mediated reductive cyclizations have provided the tricyclic core of the neodolastane natural products as confirmed by characterization of the 5–7–5 tricyclic ketone **53**. These efforts provide a basis to further our investigations toward the trichoaurantianolide natural products.

Experimental

General

Optical rotations were obtained on a PerkinElmer 241 polarimeter at 589 nm (sodium D line) using a 10 cm path length and a 1.0 mL volume. Concentrations (*c*) are given in g/100 mL. Infrared (FT-IR) spectra were recorded on a Nicolet Avatar 360 spectrometer and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were measured on a Varian VXR-400 (400 MHz), Varian INOVA-500 (500 MHz), or Varian INOVA-400 (400 MHz) instrument. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were measured on an INOVA-400 (101 MHz), VXR-400 (101 MHz), or INOVA-500 (125 MHz) spectrometer. ^1H NMR and ^{13}C NMR spectra were acquired as solutions in $CDCl_3$ and are reported in parts per million (ppm) downfield (δ) from tetramethylsilane using residual chloroform ($CHCl_3$) as an internal standard set to δ 7.26 and 77.00 ppm, respectively. Proton NMR data are reported in the following form: δ (multiplicity, coupling constants, number of protons). Mass spectral data (low-resolution mass spectrometry (LR-MS) and high-resolution (HR)-MS) were recorded on a Waters LCT Classic electrospray time-of-flight analyzer with an Agilent 1100 capillary high-performance liquid chromatography (HPLC) inlet, a Sciex API III electrospray quadropole with direct infusion inlet, or a Finnigan MAT-95 by use of chemical ionization (CI) or electron impact (EI). Analytical HPLC was performed using a Waters 600E HPLC on a Supelco Ascentis Si 5 μm (25 cm × 4.6 mm) column. Preparative HPLC was performed using a Waters LC2000 HPLC on a Supelco Ascentis Si 5 μm (25 cm × 21.2 mm) column. HPLC purifications used either a hexanes/EtOAc or hexanes/*i*-PrOH isocratic gradient, with ultraviolet (UV) detection at λ = 254 nm using a Waters 796 PDA.

Analytical TLC was performed using glass-backed 0.25 mm thickness silica gel 60 (F_{254}) plates (EM Science), which were visualized under UV light and (or) staining with ethanolic *p*-anisaldehyde, potassium permanganate, or phosphomolybdic acid. Flash chromatography was performed using Merck silica gel 60 (Kiesegel 60) (EM Science; 230–400 mesh, American Society for Testing and Materials (ASTM)) or similar products from Whatman Scientific or Sorbent Technologies, and pressure was obtained using an airline bleed.

All reagents and solvents were reagent grade and used as received unless noted otherwise. Bulk-grade hexanes and ethyl acetate (EtOAc) for chromatography were distilled before use. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were obtained anhydrous by degassing with argon and then passing through activated alumina columns under pressure to remove water and oxygen.[36] Methylene chloride (CH_2Cl_2), *N*,*N*-diisopropylamine (DIPEA), and triethylamine (Et_3N) were distilled from CaH_2 under dry air immediately before use. HMPA was stored over CaH_2 and distilled under high vacuum.

Unless otherwise noted, all reactions were conducted in flame-dried glassware under an atmosphere of argon. All nonvolatile samples were pumped to a constant weight under high vacuum (0.1–0.2 mm Hg; 1 mm Hg = 133.3224 Pa) at ambient temperature following removal of solvents by rotary evaporation.

((2R,3R)-2-(2-(tert-Butyldimethylsilyloxy)ethyl)-3-isopropyl-2-methylcyclopenty-lidene)hydrazine (16)

To a solution of (–)-**13** (1.23 g, 4.1 mmol), EtOH (50 mL), and Et_3N (13.8 mL, 98.7 mmol) was added an 85% aqueous hydrazine solution (9.92 mL, 271 mmol) and the reaction mixture was heated to reflux. After 68 h, the reaction mixture was cooled to room temperature (rt) and was partitioned between CH_2Cl_2 (200 mL) and H_2O (100 mL). The organic layer was extracted, the aqueous layer was extracted with CH_2Cl_2 (1 × 200 mL), and the organic layers were combined, washed with brine (60 mL), dried over Na_2SO_4, and concentrated in vacuo to provide a yellow oil. The crude product was purified via flash chromatography (hexanes/EtOAc, 4:1 → 3:2), providing the hydrazone **16** (1.230 g, 96%) as a clear slightly yellow oil. Hydrazone **16** is characterized as follows: $[\alpha]_D^{23}$ –29.9 (*c* 1.65, $CHCl_3$). R_f = 0.22 (30% EtOAc in hexanes). IR (neat, cm^{-1}): 3380, 3220, 2970, 2860, 1740, 1520, 1396, 1370, 1260, 1090, 840, 780. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.80 (br s, 2H), 3.68–3.53 (m, 2H), 2.36–2.28 (m, 1H), 2.05–1.90 (m, 3H), 1.83–1.60 (m, 3H), 1.50–1.38 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 3H), 0.87 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.03 (s, 3H), 0.02, (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.8, 60.2, 50.7, 46.8, 41.9, 28.6, 26.0, 24.9, 24.6, 22.8, 21.2, 21.1, 18.3, –5.2, –5.3. MS (CI, NH_3) *m*/*e* (relative intensity): 313 (1), 255 (13), 241 (8), 154 (29), 149 (24), 123 (10), 111 (100), 107 (12), 85 (25), 55 (10). HR-MS *m*/*e* calcd for $C_{12}H_{25}OS$ $[M + 1]^+$: 313.2677; found: 313.2666.

tert-Butyl(2-((1R,5R)-2-iodo-5-isopropyl-1-methylcyclopent-2-enyl)ethoxy)dimethylsilane (17)

To a 100 mL round-bottom flask was added I_2 (1.41 g, 5.57 mmol) and THF (20 mL). A solution of 1,1,3,3-tetramethylguanidine (1.81 mL, 14.4 mmol) in THF (20 mL) was added dropwise to the flask over 5 min. The reaction was stirred for 10 min at which point hydrazone **16** (300 mg, 0.960 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 30 min, Et_2O (120 mL) was added, and

the reaction mixture was washed with saturated aqueous $CuSO_4$ (2 × 60 mL). The aqueous layer was extracted with Et_2O (30 mL), and the combined organic layers were washed with saturated aqueous Na_2SO_3 (2 × 40 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo to provide a yellow oil. The crude product was purified via flash chromatography (hexanes/EtOAc, 15:1) to provide **17** (268 mg, 68%) as a clear colorless oil. R_f = 0.55 (10% EtOAc in hexanes). IR (neat, cm^{-1}): 3060, 2980, 1620, 1470, 1390, 1370, 1295, 1260, 1090, 1030, 1005, 980, 930, 900, 840, 810, 740. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.08–6.05 (m, 1H), 3.68–3.53 (m, 2H), 2.40–2.30 (m, 1H), 2.03–1.93 (m, 2H), 1.80–1.65 (m, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.7, 111.4, 60.0, 52.4, 46.9, 41.6, 37.8, 29.7, 26.0, 22.4, 21.9, 20.5, 18.2, –5.1, –5.2. MS (CI, NH_3) *m/e* (relative intensity): 351 (17), 184 (8), 149 (36), 123 (56), 121 (19), 107 (44), 93 (42), 83 (47), 49 (100). HR-MS *m/e* calcd for $C_{17}H_{33}IOSi$ $[M + H]^+$: 409.1424; found: 409.1448.

*(4*R*,5*R*)-Ethyl 5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-ene-1-carboxylate (18)*

To a solution of **17** (337 mg, 0.825 mmol) in Et_2O (3.5 mL) at –78 °C was added *n*-BuLi (2.5 mol/L in hexanes, 396 μL, 0.99 mmol) dropwise. After 30 min, ethyl chloroformate (316 μL, 3.3 mmol) was added dropwise, and the reaction was allowed to slowly warm to room temperature. After 12 h, Et_2O (6 mL) was added to the reaction mixture followed by the addition of saturated aqueous $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 mL). The organic layers were combined, washed with H_2O (6 mL), brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo to provide a clear colorless oil. The crude oil was purified by flash chromatography (hexanes/EtOAc, 10:1) to provide (4*R*,5*R*)-ethyl 5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-ene-1-carboxylate (**18**; 290 mg, 99%) as a clear colorless oil. $[\alpha]_D^{22}$ –8.2 (*c* 0.45, $CHCl_3$). R_f = 0.55 (hexanes/EtOAc, 10:1). IR (film, cm^{-1}): 2957, 1715, 1627, 1471 1368, 1236, 1096, 835, 775. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.69–6.67 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.66–3.45 (m, 2H), 2.48–2.36 (m, 1H), 2.24 (ddd, *J* = 14.2, 8.4, 5.9 Hz, 1H), 2.09–1.96 (m, 2H), 1.85–1.69 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.12 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.3, 143.0, 142.6, 61.2, 60.1, 51.4, 49.5, 40.4, 35.4, 29.4, 26.4, 23.2, 22.7, 20.8, 18.7, 14.6, –4.94 (2C). HR-MS-ESI calcd for $C_{20}H_{38}O_3SiNa$ $[M + Na^+]$: 377.2488; found: 377.2481.

*((4*R*,5*R*)-5-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methanol (19)*

To a solution of (4*R*,5*R*)-ethyl 5-(2-(*tert*-butyldimethylsilyloxy) ethyl)-4-isopropyl-5-methylcyclopent-1-ene-1-carboxylate (153 mg, 0.43 mmol) in CH_2Cl_2 (2.4 mL) at –78 °C was added diisobutylaluminum hydride (1.0 mol/L in hexanes, 1.08 mL, 1.08 mmol) dropwise. After 45 min at –78 °C, the reaction temperature was allowed to warm to –10 °C over 3 h and then was quenched with 4 mL of saturated aqueous sodium potassium tartrate (4 mL) and stirred overnight. The reaction mixture was extracted with CH_2Cl_2 (2 × 4 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to provide a clear colorless oil. The product was purified by flash chromatography (hexanes/EtOAc, 10:1) to provide ((4*R*,5*R*)-5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methanol (**19**) (108 mg, 80%) as a clear colorless oil. $[\alpha]_D^{23}$ –3.5 (*c* 2.28, $CHCl_3$). R_f = 0.19 (10% EtOAc in hexanes). IR (neat, cm^{-1}): 3381, 2955, 1472, 1254, 835. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.54 (d, *J* = 1.1 Hz, 1H), 4.11 (d, *J* = 4.3 Hz, 2H), 3.75–3.58 (m, 2H), 2.77 (t, *J* = 5.1 Hz, 1H), 2.36–2.28 (m, 1H), 2.00–1.90 (m, 2H), 1.85 (q, *J* = 8.1 Hz, 1H), 1.78–1.65 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.9, 124.9, 60.6, 59.7, 51.0, 48.8, 40.4, 34.8, 29.2, 25.9, 22.6, 22.4, 20.7, 18.3, −5.5. MS (CI, CH_4) *m/e* (relative intensity): 137 (100), 163 (71), 237 (14), 312 (2). HR-MS *m/e* calcd for $C_{18}H_{36}O_2Si$ (M^+): 312.24846; found: 312.24899. Anal. calcd for $C_{18}H_{36}O_2Si$: C 69.17, H 11.61; found: C 68.93, H 11.63.

*((4*R*,5*R*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl acetate (32)*

A solution of ((4*R*,5*R*)-5-(2-(*tert*-butyldimethylsilyloxy) ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methanol (**19**; 1.82 g, 5.83 mmol) in CH_2Cl_2 (29 mL) was cooled to 0 °C and treated with 4-dimethylaminopyridine (1 crystal), pyridine (3.76 mL, 46.6 mmol), and acetic anhydride (1.66 mL, 17.5 mmol). The cooling bath was removed and the reaction was allowed to warm to rt. After 45 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and isolated in vacuo to provide a clear colorless oil. The product was purified by flash column chromatography (hexanes/EtOAc, 20:1) to provide 1.83 g (90%) of **32** as a clear colorless oil. $[\alpha]_D^{20}$ –11.8 (*c* 6.81, $CHCl_3$). R_f = 0.65 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 2956, 2930, 2857, 1746, 1473, 1365, 1228, 1092, 1040, 939, 836. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.62 (bs, 1H), 4.62–4.51 (m, 2H), 3.69 (ddd, *J* = 10.1, 8.5, 6.1 Hz, 1H), 3.55 (ddd, *J* = 10.1, 8.8, 5.6 Hz, 1H), 2.35–2.25 (m, 1H), 2.07 (s, 3H), 2.00–1.92 (m, 1H), 1.85–1.65 (m, 4H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 3H), 0.88 (s, 9H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.8, 145.3, 127.4, 61.3, 60.4, 51.4, 49.3, 40.8, 34.7, 29.2, 26.0, 22.5, 22.3, 21.0, 20.4, 18.3, –5.3 (2C). HR-MS-ESI calcd for $C_{20}H_{38}O_3SiNa$ $[M + Na^+]$: 377.2488; found: 344.2473.

1-(2-(Hydroxymethyl)oxiran-2-yl)ethanone

To a solution of **25** (1.13 g, 11.3 mmol) in THF (40 mL) at 0 °C was added H_2O_2 (30% wt in H_2O, 5.13 g, 45.2 mmol) dropwise over 6 min, followed by benzyltrimethylammonium hydroxide (Triton B; 40% wt in MeOH, 473 mg, 1.13 mmol). The reaction mixture was stirred for 80 min and quenched slowly with solid $Na_2S_2O_3$ (16.24 g, 102.75 mmol; noted extensive gas evolution). After being quenched, the reaction mixture was brought to ambient temperature, CH_2Cl_2 (70 mL) was added, and the solution was dried over Na_2SO_4. The solids were filtered, and the filtrate was washed with CH_2Cl_2 (50 mL) and EtOAc (50 mL). Removal of the solvent in vacuo provided a slightly yellow oil. Purification of the crude material via flash chromatography (hexanes/EtOAc, 1:1) afforded 1-(2-(hydroxymethyl)oxiran-

2-yl)ethanone (912 mg, 78%) as a clear colorless oil. R_f = 0.43 (hexanes/EtOAc, 1:3). IR (film, cm^{-1}): 3445, 2929, 1666, 1362, 1222, 1045. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.00 (d, A of AB, J_{AB} = 12.7 Hz, 1H), 3.89 (d, B of AB, J_{AB} = 12.7 Hz, 1H), 3.08 (d, A of AB, J_{AB} = 5.0 Hz, 1H), 3.03 (d, B of AB, J_{AB} = 5.0 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.7, 61.6, 61.2, 48.9, 23.8. HR-MS-CI calcd for $C_5H_9O_3$ [M + H$^+$]: 117.0546; found: 117.0549.

(2-Acetyloxiran-2-yl)methyl 2-(diethoxyphosphoryl) acetate (26)

To a solution of 1-(2-(hydroxymethyl)oxiran-2-yl)ethanone (864 mg, 7.44 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 4-dimethylaminopyridine (DMAP; 45.4 mg, 0.372 mmol) followed by 2-diethylphosphonoacetic acid (1.44 mL, 8.93 mmol) and *N*,*N*′-diisopropylcarbodiimide (1.44 mL, 9.67 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The insoluble materials were filtered from the reaction mixture and the reaction mixture was concentrated in vacuo. Et_2O (60 mL) was added to the crude reaction mixture, insoluble materials were filtered, and the reaction mixture was concentrated in vacuo. This procedure was repeated three times to afford a yellow oil. Purification by flash chromatography (hexanes/EtOAc, 1:5) provided **26** (1.85 g, 85%) as a clear oil. R_f = 0.18 (hexanes/EtOAc, 1:3). IR (film, cm^{-1}): 2986, 2934, 1744, 1716, 1269, 1119, 1026, 972. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.80 (d, A of AB, J_{AB} = 12.4 Hz, 1H), 4.32 (d, B of AB, J_{AB} = 12.4 Hz, 1H), 4.16 (m, 4H), 3.15 (d, A of AB, J_{AB} = 4.9 Hz, 1H), 3.02 (d, B of AB, J_{AB} = 4.9 Hz, 1H), 3.00 (s, 1H), 2.94 (s, 1H), 2.09 (s, 3H), 1.35 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 218.3, 165.2 (d, J_{CP} = 6.2 Hz), 62.8 (d, J_{CP} = 6.3 Hz), 62.5, 60.0, 48.8, 34.1 (d, J_{CP} = 134.0 Hz), 23.7, 16.3 (d, J_{CP}= 6.2 Hz). HR-MS-ESI calcd for $C_{11}H_{19}O_7Na$ [M + Na$^+$]: 317.0766; found: 317.0758.

8-Methyl-1,5-dioxaspiro[2.5]oct-7-en-6-one (24)

To a solution of **26** (430 mg, 1.46 mmol) in acetonitrile (60 mL) at 0 °C was added LiCl (74.2 mg, 1.75 mmol) followed by dropwise addition of DBU (221.4 μL, 1.46 mmol). The white suspension was stirred for 1 h, allowed to warm to rt, and was quenched with a 50% saturated NH_4Cl solution (50 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a red oil. The crude product was purified via flash chromatography (hexanes/EtOAc, 1:1) to provide racemic **24** (181 mg, 89%) as a white solid. R_f = 0.50 (hexanes/EtOAc, 1:3). IR (film, cm^{-1}): 3064, 2991, 1731, 1639, 1446, 1398, 1270, 1231, 1151, 1104, 1061, 941, 855. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.09 (m, 1H), 4.39 (d, A of AB, J_{AB} = 12.2 Hz, 1H), 4.27 (d, B of AB, J_{AB} = 12.2 Hz, 1H), 3.15 (d, A of AB, J_{AB} = 4.4 Hz, 1H), 3.01 (d, B of AB, J_{AB} = 4.4 Hz, 1H), 1.81 (d, J = 1.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.8, 154.3, 122.0, 69.8, 53.2, 51.1, 15.7. HR-MS-CI calcd for $C_7H_9O_3$ [M + H$^+$]: 141.0546; found: 141.0546.

3-((4R,5R)-5-(2-(tert-Butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)-5-methylene-5,6-dihydro-2H-pyran-2-one (28)

To a solution of iodide **17** (143 mg, 0.348 mmol) in THF (1.5 mL) at –78 °C was added *n*-BuLi (2.5 mol/L in hexanes, 167 μL, 0.418 mmol) dropwise. After 30 min, a solution of LiCuCN(2-Th) (0.25 mol/L in THF, 1.50 mL, 0.375 mmol) was added dropwise. The reaction was stirred for 10 min at –78 °C, placed in a 0 °C ice bath for 10 min, then cooled back to –78 °C. A solution of the racemic epoxide **24** (67 mg, 0.478 mmol) in THF (2 mL) was cooled to –78 °C and was cannulated into the cuprate solution. The reaction was maintained at –50 °C for 1 h, and then was warmed to rt and was stirred overnight. The reaction was quenched with 50% saturated aqueous NH_4Cl with stirring for 15 min. The organic layer was separated and the aqueous layer was washed with EtOAc (3 × 4 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide an oil. Purification via flash chromatography (hexanes/EtOAc, 4:1) provided triene **28** (30 mg, 15%) as a white solid. R_f = 0.48 (hexanes/EtOAc, 4:1). IR (film, cm^{-1}): 2974, 2949, 2855, 1702, 1471, 1389, 1276, 1091, 836. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.54 (t, J = 2.4 Hz, 1H), 5.43(s, 1H), 5.36 (s, 1H), 4.82 (s, 2H), 3.71–3.57 (m, 2H), 2.49–2.40 (m, 1H), 2.25–2.16 (m, 1H), 2.04 (s, 3H), 1.97–1.76 (m, 2H), 1.67 (t, J = 7.4 Hz, 2H), 1.01–0.99 (m, 6H), 0.94 (d, J = 6.5 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.7, 147.1, 144.8, 138.0, 131.5, 127.2, 115.4, 69.6, 60.4, 53.0, 52.8, 42.9, 33.9, 28.7, 26.0, 23.1, 20.9, 19.5, 18.3, 16.9, –5.2. HR-MS-CI calcd for $C_{24}H_{41}O_3Si$ [M + H$^+$]: 405.2819; found: 405.2811.

4-Methyl-1-oxaspiro[2.5]octan-6-one (27)

To a solution of **24** (79 mg, 0.056 mmol) in benzene (1.7 mL) was added $(PPh_3)_2RhCl$ (10 mg, 0.011 mmol). The reaction flask was put in a reaction bomb, charged with 50 bar H_2, and reacted over 18 h at rt. After purging the reaction flask with argon, the solvent was removed in vacuo and the crude product was purified via flash column chromatography (hexanes/EtOAc, 1:1) to afford 74 mg (92%) of **27** as a clear yellow oil as a 60:40 mixture of inseparable diastereomers. R_f = 0.44 (hexanes/EtOAc, 1:3). IR (thin film, cm^{-1}): 2973, 2942, 1741, 1460, 1420, 1379, 1354, 1274, 1185, 1153, 1047. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.57 (d, J = 12.7 Hz, 0.4H), 4.53 (d, J = 12.5 Hz, 0.6H), 4.08 (d, J = 12.5 Hz, 0.6H), 4.07 (d, J = 12.7 Hz, 0.4H), 2.97–2.90 (m, 1.37H), 2.81–2.68 (m, 1.70H), 2.55–2.42 (m, 1.61H), 2.10–2.01 (m, 0.47H), 1.14 (d, J = 7.1 Hz, 1.15H), 0.91 (m, 1.84H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.9, 169.8, 72.9, 71.2, 57.6, 56.3, 49.6, 49.2, 36.4, 36.3, 31.4, 28.3, 16.8, 13.5. GC-HR-MS calcd for $C_7H_{11}O_3$ [M + H$^+$]: 143.0703; found: 143.0707.

(Z)-Ethyl 4-(benzyloxy)-3-(tributylstannyl)but-2-enoate (30)

A suspension of CuCN (1.36 g, 15.2 mmol) in THF (52 mL) was cooled to –78 °C and treated with *n*-BuLi (2.5 mol/L in hexanes, 12.2 mL, 30.4 mmol) dropwise. The resulting yellow heterogeneous solution was warmed to 0 °C and stirred for 30 min. The suspension became a clear yellow solution. The solution was then cooled to –78 °C and treated with neat *n*-Bu_3SnH (8.85 g, 30.4 mmol) dropwise over 10 min with a noted color change to a dark yellow solution with H_2 evolution. After 10 min, ethyl ester **29** (3.01 g, 13.8 mmol) in THF (6 mL) was added dropwise and the reaction turned a dark red color. After 10 min, the reaction mixture was quenched by cannulation into a 90% saturated aqueous NH_4Cl / 10% NH_4OH solution (200 mL). After 45 min, the layers were separated and the aqueous layer was washed with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo

to provide a brown oil. The crude product was purified by flash column chromatography (petroleum ether / Et_2O, 99:1) to provide **30** (6.00 g, 86%) as a clear colorless oil. R_f = 0.55 (hexanes/EtOAc, 10:1). IR (film, cm^{-1}): 2955, 2870, 1702, 1604, 1456, 1307, 1194. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 6.75 (t, J = 2.1 Hz, $J_{Sn–H}$ = 52 Hz, 1H), 4.56 (s, 2H), 4.31 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 1.51–1.27 (m, 15H), 1.08–0.84 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.2, 168.0, 138.2, 128.4, 127.6, 127.5, 126.3, 75.5, 72.5, 60.3, 29.2, 27.4, 14.3, 13.7, 10.9. HR-MS-ESI calcd for $C_{25}H_{42}O_3SnNa$ [M + Na^+]: 533.2054; found: 533.2073.

(E)-Ethyl 4-(benzyloxy)-3-(tributylstannyl)but-2-enoate (31)

A suspension of CuCN (88 mg, 1 mmol) in THF (3 mL) was cooled to –78 °C and treated with *n*-BuLi (2.1 mol/L in hexanes, 1.05 mL, 2.2 mmol) dropwise. The resulting yellow heterogeneous solution was warmed by removal of the cold bath until the reaction mixture became a clear yellow solution. The solution was then cooled to –78 °C and treated with neat *n*-Bu_3SnH (640 mg, 2.2 mmol) dropwise with a noted color change to a dark yellow solution with H_2 evolution. After 15 min, a solution of ester **29** (328 mg, 1 mmol) in THF (2 mL) and MeOH (202 μL, 5 mmol) was added dropwise and the reaction turned a dark red color. After 15 min, the reaction mixture was quenched by the addition of a 90% saturated aqueous NH_4Cl / 10% NH_4OH solution (10 mL) at –78 °C and warmed to rt. After 1 h, Et_2O (15 mL) was added and the phases were separated. The aqueous layer was washed with Et_2O (2 × 15 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a clear colorless oil. The crude product was purified by flash column chromatography (petroleum ether / Et_2O, 97:3) to provide **31** (302 mg, 59%) as a clear colorless oil. R_f = 0.50 (hexanes/EtOAc, 10:1). IR (film, cm^{-1}): 3032, 2957, 2854, 1709, 1606, 1456, 1344, 1179, 1093, 864. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.26 (m, 5H), 5.90 (t, J = 2.6 Hz, $J_{Sn–H}$ = 31.2 Hz, 1H), 4.71 (m, 2H), 4.54 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 1.52–1.20 (m, 15H), 0.95–0.78 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.0, 164.4, 138.1, 128.2, 128.1, 127.6, 124.0, 74.4, 73.0, 59.8, 29.1, 29.0, 27.3, 14.3, 13.7, 10.9. HR-MS-ESI calcd for $C_{25}H_{42}O_3SnNa$ [M + Na^+]: 533.2054; found: 533.2048.

(E)-Ethyl 4-(benzyloxy)-3-(((4R,5R)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl)but-2-enoate (33)

To a 100 mL round-bottom flask, LiCl (345 mg, 8.14 mmol) was added and was flame-dried under a stream of argon. Upon cooling, $Pd(PPh_3)_4$ (157 mg, 0.136 mmol) and CuCl (671 mg, 6.78 mmol) were added to the flask. After flushing the flask with argon for several minutes, a solution of allylic acetate **32** (481 mg, 1.36 mmol) in dimethyl sulfoxide (DMSO; 13.6 mL) was added followed by the vinyl stannane **30** (967 mg, 1.90 mmol) in DMSO (13.6 mL). The resulting reaction mixture was degassed (3×) by the freeze–pump–thaw method. The reaction was stirred for 1 h, and then heated to 50 °C for 13 h. After cooling to rt, the reaction was transferred to a separatory funnel and water (200 mL) and Et_2O (60 mL) were added. The organic layer was separated and then the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a brown oil. The crude product was purified by flash column chromatography (hexanes/EtOAc, 30:1) to afford **33** (594.2 mg, 85%) as a clear colorless oil. $[\alpha]_D^{20}$ –21.5 (*c* 0.69, $CHCl_3$). R_f = 0.68 (hexanes/EtOAc, 4:1). IR (film, cm^{-1}): 2955, 2856, 1718, 1659, 1472, 1255, 1178, 1095, 836. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 5H), 6.16 (bs, 1H), 5.14 (bs, 1H), 4.54 (ABq, $\Delta\nu_{AB}$ = 9.6 Hz, J_{AB} = 12 Hz, 2H), 4.16 (d, J = 7 Hz, 2H), 4.00 (dq, J = 15.1, 1.5 Hz, 2H), 3.72 (td, J = 9.7, 6.4, 1H), 3.56 (td, J = 9.9, 4.9 Hz, 1H), 3.20 (dd, J = 15.7, 2.1 Hz, 1H), 3.11 (d, J = 15.7, 1H), 2.26–2.19 (m, 1H), 1.89–1.64 (m, 5H), 1.27 (t, J = 7.1 Hz, 3H), 1.00 (d, J = 7.7 Hz, 3H), 0.93 (s, 3H), 0.89 (s, 9H), 0.86 (d, J = 6.5 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 166.1, 155.6, 147.0, 137.9, 128.4, 127.7, 127.6, 122.6, 116.5, 72.6, 72.5, 60.5, 59.7, 51.2, 49.9, 40.7, 34.5, 29.3, 27.3, 26.0, 22.6, 22.3, 19.9, 14.3, –5.2 (2C). HR-MS-ESI calcd for $C_{31}H_{50}O_4SiNa$ [M + Na^+]: 537.3376; found: 537.3365.

(Z)-Ethyl 4-(benzyloxy)-3-(((4R,5R)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl)but-2-enoate (34)

To a small flask, LiCl (19.3 mg, 0.457 mmol) was added and flame-dried under a stream of argon. Upon cooling, $Pd(PPh_3)_4$ (8.8 mg, 7.6 μmol) and CuCl (38 mg, 0.38 mmol) were added to the flask. After flushing the reaction flask with argon for several minutes, a solution of allylic acetate **32** (27 mg, 0.076 mmol) in DMSO (0.7 mL) was added followed by vinyl stannane **31** (54.2 mg, 0.107 mmol) in DMSO (0.8 mL). The resulting reaction mixture was degassed (3×) by the freeze–pump–thaw method. The reaction was stirred for 1 h at rt and then heated to 50 °C for 13 h. After cooling to rt, the reaction was transferred to a separatory funnel and water (20 mL) and Et_2O (20 mL) were added. The organic layer was separated and then the aqueous layer was washed with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a brown oil. The crude product was purified by flash column chromatography (Et_2O / petroleum ether, 3:97) to afford **34** (29.0 mg, 67%) in about 90% purity (as judged by evidence in the ^1H NMR spectrum with approximately 5%–10% of an inseparable side product) as a clear colorless oil. R_f = 0.67 (hexanes/EtOAc, 4:1). IR (film, cm^{-1}): 2956, 2928, 2856, 1716, 1643, 1497, 1463, 1374, 1255, 1215, 1146, 1093. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.26 (m, 5H), 5.81 (s, 1H), 5.23 (s, 1H), 4.63 (ABq, $\Delta\nu_{AB}$ = 49 Hz, J_{AB} = 13.6 Hz, 2H), 4.50 (ABq, $\Delta\nu_{AB}$ = 6 Hz, J_{AB} = 12 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.73–3.61 (m, 1H), 3.50 (td, J = 9.7, 5.2 Hz, 1H), 2.90 (ABq, $\Delta\nu_{AB}$ = 29 Hz, J_{AB} = 15.8, 2H), 2.28–2.22 (m, 1H), 1.94–1.59 (m, 5H), 1.27 (t, J = 7.1 Hz, 3H), 1.01 (d, J = 5.8 Hz, 3H), 0.89–0.83 (m, 15H), 0.03 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 166.0, 157.7, 147.3, 138.3, 128.3, 127.7, 127.5, 124.6, 119.3, 72.6, 67.4, 60.5, 59.9, 51.1, 50.1, 40.7, 34.6, 32.6, 29.3, 26.0, 22.6, 22.3, 20.0, 18.3, 14.3, –5.2 (2C). HR-MS-ESI calcd for $C_{31}H_{50}O_4SiNa$ [M + Na^+]: 537.3376; found: 537.3358. This material was used without the need for additional purification.

(E)-4-(Benzyloxy)-3-(((4R,5R)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl)but-2-en-1-ol

A solution of **33** (156.4 mg, 0.304 mmol) in CH_2Cl_2 (6.2 mL) was cooled to –78 °C and treated with diisobutylaluminium hydride

(DIBAL-H; 760 μL, 1 mol/L in hexanes, 0.760 mmol). After 1 h at –78 °C, additional DIBAL-H was added (304 μL, 1 mol/L in hexanes, 0.304 mmol). After 30 min, the reaction was warmed to –15 °C over 1.5 h and then quenched with saturated aqueous Rochelle's salt (6 mL). The reaction was warmed to rt and stirred for 2 h after which the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL), and the organic layers were combined. The organic layer was washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to provide a yellow oil. The crude product was purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford the expected (*E*)-allylic alcohol (132.4 mg, 92%) as a clear colorless oil. R_f = 0.26 (hexanes/EtOAc, 4:1). $[\alpha]_D^{20}$ –19.7 (*c* 3.10, $CHCl_3$). IR (film, cm^{-1}): 3384, 2954, 2929, 1471, 1255, 1094, 1006. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.26 (m, 5H), 5.85 (t, *J* = 6.8 Hz, 1H), 5.20 (s, 1H), 4.49 (ABq, $\Delta\nu_{AB}$ = 17 Hz, J_{AB} = 11.9 Hz, 2H), 4.23–4.10 (m, 1H), 3.92 (ABq, $\Delta\nu_{AB}$ = 32 Hz, J_{AB} = 12.2 Hz, 2H), 3.70 (td, *J* = 9.7, 6.5 Hz, 1H), 3.45 (td, *J* = 10.0, 4.7 Hz, 1H), 2.70 (ABq, $\Delta\nu_{AB}$ = 23 Hz, J_{AB} = 16.5 Hz, 2H), 2.25–2.19 (m, 1H), 1.89–1.53 (m, 5H), 1.01 (d, *J* = 5.9 Hz, 3H), 0.91 (s, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 5.9 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.8, 138.3, 137.3, 128.3, 127.6, 127.5, 127.4, 123.6, 73.4, 72.2, 60.7, 59.2, 51.4, 49.8, 40.5, 24.5, 29.4, 26.0, 25.9, 22.6, 22.3, 19.9, 18.4, –5.2 (2C). HR-MS-ESI calcd for $C_{29}H_{48}O_3SiNa$ [M + Na^+]: 495.3270; found: 495.3274.

((2S,3S)-3-(Benzyloxymethyl)-3-(((4R,5R)-5-(2-(tert-butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methyl)oxiran-2-yl)methanol (35)

A heterogeneous solution of L-DIPT (152 mg, 0.65 mmol), CH_2Cl_2 (8 mL), and 4 Å powdered molecular sieves (95 mg) was cooled to –20 °C and treated with Ti(O-*i*-Pr)$_4$ (148 μL, 0.5 mmol) dropwise. After 30 min, *t*-BuOOH (559 μL, 3.6 mol/L in toluene, 1.64 mmol) was added dropwise. After an additional 30 min, the starting (*E*)-allylic alcohol from ester **33** was added as a solution (473 mg, 1 mmol) in CH_2Cl_2 (5 mL) via syringe followed by a CH_2Cl_2 (5 mL) syringe wash. The reaction was allowed to stir for 20 h at –20 °C and was quenched with a 30% aqueous NaOH solution saturated with NaCl (740 μL) followed by H_2O (2 mL). The reaction was warmed to rt and stirred for 40 min. The mixture was then filtered through Celite, and the filtrate was washed with H_2O (10 mL) and CH_2Cl_2 (10 mL). The organic layer was then separated and the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide a cloudy yellow oil containing a 65:35 mixture of epoxy alcohol diastereomers (Table 1, entry 4). The product was purified by flash column chromatography (hexanes/EtOAc, 5:1) to provide small amounts of the major diastereomer (10 mg), the minor diastereomer epoxide (2 mg), and combined mixed fractions (331 mg, 70% overall yield) as a 65:35 mixture of epoxy alcohol diastereomers **35**. Data for the sample of the major epoxide diastereomer of **35**: $[\alpha]_D^{20}$ –26.2 (*c* 0.69, $CHCl_3$). R_f = 0.24 (hexanes/EtOAc, 4:1). IR (film, cm^{-1}): 3439, 2955, 2866, 1472, 1363, 1256, 1098. ^1H NMR (400 MHz) δ: 7.35–7.26 (m, 5H), 5.33 (s, 1H), 4.53 (ABq, $\Delta\nu_{AB}$ = 19 Hz, J_{AB} = 12.0 Hz, 2H), 3.84–3.78 (m, 1H), 3.77 (d, *J* = 11.2 Hz, 1H), 3.71–3.62 (m, 2H), 3.43–3.38 (m, 1H), 3.39 (d, *J* = 11.3 Hz, 1H), 3.27 (dd, *J* = 6.5, 4.7 Hz, 1H), 2.61 (d, *J* = 17.3 Hz, 1H), 2.33–2.18 (m, 1H), 1.96–1.66 (m, 5H), 1.60 (ddd, *J* = 14.1, 8.9, 4.9, 1H), 1.01 (d, *J* = 5.9 Hz, 3H), 0.93 (m, 15H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.4, 138.0, 128.3, 127.6, 123.8, 73.3, 71.4, 62.7, 61.0, 60.4, 59.5 50.7, 50.1, 40.4, 34.9, 29.3, 27.1, 26.0, 22.5, 22.3, 19.5, 18.3, –5.2, –5.3. HR-MS-ESI calcd for $C_{29}H_{48}O_4SiNa$ [M + Na^+]: 511.3220; found: 511.3200. Data for the sample of the minor diastereomer of **35**: R_f = 0.20 (hexanes/EtOAc, 4:1). ^1H NMR (400 MHz) δ: 7.34–7.28 (m, 5H), 5.37 (s, 1H), 4.55 (ABq, $\Delta\nu_{AB}$ = 8 Hz, J_{AB} = 12.1 Hz, 2H), 3.79–3.73 (m, 1H), 3.72 (d, *J* = 11.3 Hz, 1H), 3.68–3.58 (m, 2H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.48–3.43 (m, 1H), 3.31 (dd, *J* = 6.8, 4.6 Hz, 1H), 2.59–2.54 (m, 1H), 2.32–2.24 (m, 1H), 1.95–1.51 m, 6H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.89–0.84 (m, 15H), 0.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.6, 137.9, 128.4, 127.6, 127.6, 123.2, 73.4, 71.6, 62.7, 61.1, 60.3, 59.2, 50.7, 50.1, 40.6, 34.7, 29.2, 27.2, 26.0, 22.6, 22.1, 19.8, 18.3, –5.2 (2C). HR-MS-ESI calcd for $C_{29}H_{48}O_4SiNa$ [M + Na^+]: 511.3220; found: 511.3203.

(Z)-4-(Benzyloxy)-3-(((4R,5R)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl)but-2-en-1-ol

A solution of **34** (378 mg, 0.73 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C and treated with DIBAL-H (1.84 mL, 1 mol/L in hexanes, 1.84 mmol). After 2.5 h at –78 °C, the reaction was quenched with saturated aqueous Rochelle's salt (20 mL). The reaction was warmed to rt and stirred overnight, after which the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 15 mL), and the organic layers were combined. The organic layer was washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to provide a yellow oil. The crude product was purified by flash column chromatography (Et_2O / petroleum ether, 1:1) to provide the expected (*Z*)-allylic alcohol from **34** (283 mg, 82%) in approximately 85% purity as a clear colorless oil (approximately 10%–15% of an inseparable alkane side product was estimated by ^1H NMR spectra). R_f = 0.26 (hexanes/EtOAc, 4:1). IR (film, cm^{-1}): 3422, 3031, 2955, 2857, 1472, 1364, 1255, 1091, 1005. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.27 (m, 5H), 5.78 (t, *J* = 7.1 Hz, 1H), 5.22 (s, 1H), 4.49 (ABq, $\Delta\nu_{AB}$ = 12 Hz, J_{AB} = 12 Hz, 2H), 4.20–4.10 (m, 2H), 4.00 (ABq, $\Delta\nu_{AB}$ = 27 Hz, J_{AB} = 11.1 Hz, 2H), 3.68 (td, *J* = 9.8, 6.4 Hz, 1H), 3.43 (td, *J* = 10.1, 4.8, 1H), 2.73 (ABq, $\Delta\nu_{AB}$ = 30 Hz, J_{AB} = 16.0 Hz, 2H), 2.25–2.20 (m, 1H), 2.13–2.10 (m, 1H), 1.89–1.63 (m, 5H), 1.00 (d, *J* = 5.9 Hz, 3H), 0.90–0.85 (m, 15H), 0.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.9, 138.1, 137.9, 130.6, 128.4, 127.8, 127.7, 124.6, 72.5, 67.2, 60.7, 58.7, 51.1, 49.9, 40.5, 34.6, 34.2, 29.3, 26.0, 22.6, 22.4, 20.1, 18.3, –5.1, –5.2. HR-MS-ESI calcd for $C_{29}H_{48}O_3SiNa$ [M + Na^+]: 495.3270; found: 495.3275. This material was utilized without the need for additional purification.

((2R,3S)-3-((Benzyloxy)methyl)-3-(((4R,5R)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl)oxiran-2-yl)methanol (36)

A heterogeneous solution of D-DIPT (30 mg, 0.127 mmol), CH_2Cl_2 (1 mL), and 4 Å powdered molecular sieves (100 mg) was cooled to –25 °C and treated with Ti(O-*i*-Pr)$_4$ (31.3 μL, 0.106 mmol) dropwise. The mixture was stirred for 30 min, followed by the addition of *t*-BuOOH (90 μL, 3.58 mol/L in toluene, 0.317 mmol). After an additional 30 min, a solution of the (*Z*)-allylic alcohol (100 mg, 0.212 mmol) in CH_2Cl_2

(500 μL) was added via syringe followed by a CH_2Cl_2 (500 μL) syringe wash. The reaction was warmed to –18 °C and stirred for 17 h. The reaction was quenched at –20 °C via the addition of a 30% aqueous NaOH solution saturated with NaCl (400 μL). The reaction was warmed to rt and CH_2Cl_2 (1 mL) and H_2O (1 mL) were added, and the mixture was vigorously stirred for 1 h. The aqueous phase was washed with CH_2Cl_2 (2 × 2 mL), and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to provide clear colorless oil. The product was purified by flash column chromatography (hexanes/EtOAc, 20:1) to provide epoxide **36** (75 mg, 75%) as a 92:8 mixture of inseparable diastereomers. $[\alpha]_D^{20}$ +2.0 (*c* 0.45, $CHCl_3$). R_f = 0.46 (hexanes/EtOAc, 2:1). Data for the major diastereomer **36**: IR (film, cm^{-1}): 3431, 2955, 2929, 2856, 1454, 1255, 1091. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.30 (m, 5H), 5.43 (s, 1H), 4.7 (ABq, $\Delta\nu_{AB}$ = 12 Hz, J_{AB} = 12.0 Hz, 2H), 3.92–3.82 (m, 2H), 3.73–3.57 (m, 4H), 3.49–3.38 (m, 2H), 3.09 (t, *J* = 6.2 Hz, 1H), 2.29 (ABq, $\Delta\nu_{AB}$ = 80 Hz, J_{AB} = 16.4 Hz, 2H), 2.29–2.26 (m, 2H), 1.95–1.89 (m, 1H), 1.83–1.59 (m, 4H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.88–0.87 (m, 15H), 0.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 145.4, 137.4, 128.5, 127.9, 127.8, 125.2, 73.6, 70.0, 61.6 (2C), 61.3, 60.5, 50.7, 49.8, 40.4, 34.9, 32.4, 29.3, 26.0, 22.6, 22.3, 19.7, 18.3, –5.2 (2C). HR-MS-ESI calcd for $C_{29}H_{48}O_4SiNa$ [M + Na^+]: 511.3220; found: 511.3212.

*(2-((1**R**,5**R**)-2-(((2**S**,3**R**)-2-(Benzyloxymethyl)-3-(bromomethyl)oxiran-2-yl)methyl)-5-isopropyl-1-methylcyclopent-2-enyl)ethoxy)*(tert-*butyl)dimethylsilane (37)*

To a solution of the epoxide **35** (322.6 mg, 0.68 mmol) in CH_2Cl_2 (14 mL) at 0 °C was added imidazole (278 mg, 4.08 mmol) and PPh_3 (677 mg, 2.04 mmol), and this was followed by the addition of CBr_4 (677 mg, 2.04 mmol). The reaction was protected from light and was stirred for 2 h at which time the solvent was removed in vacuo to provide a white solid. The crude product was immediately purified by flash column chromatography (hexanes/EtOAc, 20:1) affording bromides **37** (330 mg, 88%) as a 55:45 ratio of inseparable diastereomers as a clear yellow oil starting from the mixture of epoxy alcohols (Table 1, entry 3). Similarly, the epoxide **36** was transformed to the corresponding mixture of bromides (dr 90:10). The crude epoxy bromides were characterized as follows: R_f = 0.68 (hexanes/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.27 (m, 5H), 5.41–5.39 (m 1H), 4.59–4.48 (m, 2H), 3.72–3.28 (m, 7H), 2.54–2.46 (m, 1H), 2.32–2.24 (m, 1H), 2.05–1.55 (m, 6H), 1.00 (d, *J* = 6.0 Hz, 3H), 0.89–0.86 (m, 15H), 0.03 (m, 6H). HR-MS-ESI calcd for $C_{29}H_{47}O_3BrSiNa$ [M + Na^+]: 573.2376; found: 573.2490. The bromides were not stored and were immediately used in the subsequent reaction. Comparable results were obtained by using the epoxy alcohol **36**.

*(**R**)-1-(Benzyloxy)-2-(((4**R**,5**R**)-5-(2-(*tert-*butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methyl)but-3-en-2-ol (38)*

A solution of diastereomeric bromides **37** (646 mg, 117 mmol) in THF (20 mL) was cooled to –95 °C in a hexanes/N_2(l) bath and treated with *n*-BuLi (703 μL, 2.50 mol/L in hexanes, 1.76 mmol) dropwise. The reaction was stirred for 25 min with a cooling bath temperature no higher than –85 °C and then allowed to warm to –78 °C at which point the reaction was quenched with a pH 7 buffer (4 mL) and warmed to rt. Water (30 mL) and CH_2Cl_2 were added to the reaction mixture, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to provide a clear yellow oil. Purification by flash column chromatography (hexanes/EtOAc, 15:1) provided the alcohols **38** (482 mg, 87%) as a 58:42 mixture of inseparable diastereomers as a clear colorless oil originating from the Sharpless epoxidation (Table 1, entry 3). This mixture of diastereomers was characterized as follows: R_f = 0.32 (hexanes/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.26 (m, 5H), 5.95 (dd, *J* = 17.3, 10.8 Hz, 0.42H), 5.92 (dd, *J* = 17.3, 10.8 Hz, 0.58 H), 5.62 (s, 1H), 5.40 (dd, *J* = 17.4, 1.3 Hz, 0.58 H), 5.35 (dd, *J* = 17.4, 1.2 Hz, 0.42H), 5.19 (dd, *J* = 10.6, 1.4 Hz, 0.58H), 5.18 (dd, *J* = 10.8, 1.2 Hz, 0.42H), 4.61–4.54 (m, 2H), 3.66 (td, *J* = 9.7, 6.2 Hz, 1H), 3.50–3.39 (m, 3H), 2.55 (s, 0.58H), 2.49 (s, 0.42H), 2.36–2.09 (m, 3H), 1.93–1.89 (m, 1H), 1.82–1.58 (m, 4H), 1.01–1.00 (m, 3H), 0.88–0.84 (m, 15H), 0.04 (6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.6, 144.4, 142.2, 141.9, 138.1, 138.0, 128.4, 127.6 (3C), 125.0, 124.9, 114.3, 114.2, 77.0, 76.8, 74.8 (2C), 73.5, 60.5 (2C), 50.6, 50.5, 50.3 (2C), 40.7, 35.0 (2C), 34.4, 34.3, 29.3, 29.2, 26.0, 22.7, 22.3, 22.2, 19.9, –5.2 (4C). HR-MS-ESI calcd for $C_{29}H_{48}O_3SiNa$ [M + Na^+]: 495.3270; found: 495.3290. In a similar fashion, the mixture of **36** (Table 1, entry 5) gave rise to an enriched sample of **38** (dr 91:9).

*1-(Benzyloxy)-2-(((4**R**,5**R**)-5-(2-(*tert-*butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methyl)but-3-en-2-yl acrylate (39)*

A solution of alcohol **38** (240 mg, 0.51 mmol) in THF (5.1 mL) was treated by the dropwise addition of isopropylmagnesium chloride (1.68 mol/L in Et_2O, 332 μL, 0.558 mmol), and the mixture was stirred for 30 min. Then, freshly distilled acryloyl chloride (248 μL, 3.05 mmol) was added dropwise and the colorless solution turned a yellow color. The reaction was stirred for an additional 16 h at rt and was then cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (10 mL). After warming to rt, CH_2Cl_2 (10 mL) and water (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a clear yellow oil. Purification by flash column chromatography (hexanes/EtOAc, 30:1) provided the ester **39** (187 mg, 70%, 81% brsm) as a 58:42 mixture of inseparable diastereomers and recovered allyl alcohol **38** (34 mg, 11%). The mixture of diastereomers was characterized as follows: R_f = 0.45 (hexanes/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.26 (m, 5H), 6.37–6.31 (m, 1H), 6.14–6.00 (m, 2H), 5.80–5.77 (m, 1H), 5.45 (bs, 1H), 5.31–5.20 (m, 2H), 4.54–4.53 (m, 2H), 3.93–3.82 (m, 2H), 3.67–3.61 (m, 1H), 3.51–3.41 (m, 1H), 2.83–2.77 (m, 1H), 2.54–2.49 (m, 0.40H), 2.43 (d, *J* = 16.9 Hz, 0.60H), 2.25–2.19 (m, 1H), 1.89–1.55 (m, 5H), 0.99 (d, *J* = 5.9 Hz, 3H), 0.89–0.88 (m, 9H), 0.85–0.83 (m, 6H), 0.03–0.02 (m, 6H). HR-MS-ESI calcd for $C_{32}H_{50}O_4SiNa$ [M + Na^+]: 549.3376; found: 549.3386. Similarly, the alcohol **38** (Table 1, entry 5) led to the desired ester **39** as a 92:8 ratio of C_2 diastereomers.

5-(Benzyloxymethyl)-5-(((4R,5R)-5-(2-(tert-butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methyl)furan-2(5H)-one (40)

To a solution of **39** (163 mg, 0.31 mmol) in toluene (15.5 mL) at 70 °C was added a solution of Grubbs II catalyst[25] (26.2 mg, 30.9 μmol) in toluene (3.1 mL) portionwise (500 μL) at hourly intervals via microsyringe. After an additional 90 min of stirring, the reaction was cooled to rt, and the solvent was removed in vacuo to provide a brown oil. The product was purified by flash column chromatography (hexanes/EtOAc, 20:1) to provide **40** (154 mg, 99%) as a 52:48 mixture of inseparable diastereomeric lactones originating from the epoxy alcohols (Table 1, entry 3). Similar results from the epoxide **36** (Table 1, entry 5) led to a 92:8 ratio of lactones **40**. The mixture of diastereomers was characterized as follows: R_f = 0.28 (hexanes/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, J = 5.7 Hz, 0.48H), 7.39 (d, J = 5.7 Hz, 0.52H), 7.36–7.26 (m, 5H), 6.10 (d, J = 5.4 Hz, 0.48 H), 6.09 (d, J = 5.6 Hz, 0.52H), 5.54 (s, 0.48H), 5.51 (s, 0.52H), 4.57–4.48 (m, 2H), 3.76 (d, J = 9.7 Hz, 0.48H), 3.73 (d, J = 9.9 Hz, 0.52H), 3.66 (m, 1H), 3.55 (d, J = 9.8 Hz, 0.52H), 3.51 (d, J = 9.9 Hz, 0.48H), 3.45–3.36 (m, 1H), 2.57–2.22 (m, 3H), 1.94–1.85 (m, 1H), 1.84–1.51 (m, 4H), 1.00–0.97 (m, 3H), 0.88–0.83 (m, 15H), 0.03–0.02 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.4, 172.3, 158.7, 158.0, 142.6, 142.2, 137.4, 128.5, 127.9, 127.7, 127.6, 126.8, 126.6, 122.2, 122.0, 90.0, 89.9, 73.8, 73.0, 72.7, 60.4, 60.3, 50.6, 50.5, 50.2, 41.0, 40.8, 34.9, 34.8, 30.9, 30.8, 29.3, 29.2, 26.0 (2C), 22.7 (2C), 22.2, 22.0, 20.2, 19.8, 18.3, –5.2 (2C), –5.3. LR-MS-ESI calcd for $C_{30}H_{46}O_4Si$ [M + H^+]: 499.3; found: 499.2.

5-(Benzyloxymethyl)-5-(((4R,5R)-5-(2-(tert-butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methyl)-4-methyldihydrofuran-2(3H)-one (41)

A hetereogeneous solution of CuI (52.3 mg, 0.28 mmol) in Et_2O (1.4 mL) was cooled to 0 °C and treated with methyllithium (344 μL, 1.6 mol/L in Et_2O, 0.55 mmol) dropwise. The turbid brown solution became a clear colorless solution within 5 min. After stirring for 30 min, the reaction was cooled to –25 °C, and a solution of **40** (55 mg, 0.11 mmol) in Et_2O (0.5 mL) was introduced by syringe. After 90 min at –20 °C, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) at –20 °C and stirred for 30 min at rt. H_2O (2 mL) and EtOAc (6 mL) were added to the mixture and the organic layer was separated. The aqueous layer was washed with EtOAc (3 × 15 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to provide a yellow oil. The product was purified by flash column chromatography (hexanes/EtOAc, 10:1) to provide the expected 3-methyl-butyrolactone (49 mg) as a 58:42 mixture of two diastereomers in an 86% yield as a clear colorless oil. Data characterizing the less polar conjugate addition product: R_f = 0.32 (hexanes/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 5.67 (s, 0.68H), 5.60 (0.32H), 4.56–4.42 (m, 2H), 3.68–3.51 (m, 3H), 3.44–3.38 (m, 1H), 2.59–2.47 (m, 3H), 2.35–2.20 (m, 2.68H), 2.05 (d, J = 16.6 Hz, 0.32H), 1.95–1.90 (m, 1H), 1.81–1.68 (m, 3H), 1.60–1.55 (m, 1H), 1.16–1.12 (m, 3H), 1.00–0.99 (m, 3H) 0.88–0.84 (m, 15H), 0.03 (s, 6H). HR-MS-ESI calcd for $C_{31}H_{50}O_4Na$ [M + Na^+]: 537.3376; found: 537.4540. Characterization data for the more polar diastereomer: R_f = 0.24 (hexanes/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 5.60 (s, 0.5H), 5.43 (s, 0.5H), 4.55–4.45 (m, 2H), 3.74–3.40 (m, 4H), 3.00–2.88 (m, 1H), 2.78–2.71 (m, 1H), 2.33–2.11 (m, 4H), 1.93–1.89 (m, 1H), 1.83–1.70 (m, 3H), 1.63–1.56 (m, 1H), 1.12–1.08 (m, 3H), 1.00–0.99 (m, 3H), 0.89 (m, 15H), 0.03–0.02 (m, 6H). HR-MS-ESI calcd for $C_{31}H_{50}O_4Na$ [M + Na^+]: 537.3376; found: 537.4648.

A solution of the conjugate addition products (195 mg, 0.379 mmol) in THF (7.6 mL) was cooled to –78 °C and was then treated with freshly prepared lithium diisopropylamide (LDA; 1 mol/L in THF, 454 μL, 0.454 mmol) by dropwise addition. After 35 min, phenylselenenyl bromide (224 mg, 0.948 mmol) in THF (500 μL) was introduced by syringe. After 2.5 h, the reaction was quenched with saturated aqueous NH_4Cl (6 mL) at –78 °C and allowed to warm to rt. Water (6 mL) and Et_2O (20 mL) were added and the organic layer was extracted. The aqueous layer was washed with Et_2O (3 × 20 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a yellow oil. The product was purified via flash column chromatography (hexanes/EtOAc, 20:1) to provide the mixture of α-phenylselenolactones (224 mg, 88%) as a mixture of inseparable diastereomers. R_f = 0.70 (hexanes/EtOAc, 4:1). LR-MS-ESI calcd for $C_{37}H_{55}O_4SeSi$ [M + H^+]: 671.3; found: 671.3.

The mixture of crude α-phenylselenolactones was directly submitted for oxidative elimination. A solution of lactone diastereomers (97.2 mg, 0.145 mmol) in CH_2Cl_2 (7.3 mL) was cooled to –78 °C and was treated with a solution of *meta*-chloroperoxybenzoic acid (mCPBA; 27.5 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) by dropwise addition. After 1 h at –78 °C, Et_3N (30 μL, 0.218 mmol) was added and the mixture was allowed to warm to rt overnight. Water was added to the reaction, and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (3 × 6 mL), and the organic extracts were combined, dried over Na_2SO_4,, and concentrated in vacuo to provide a yellow oil. The crude product was purified by flash column chromatography (hexanes/EtOAc, 20:1) to provide **41** and **42** (55.4 mg, 75%) as an inseparable mixture of C_2 diastereomers (dr 58:42). In the case of samples that were independently processed from the Sharpless epoxidation leading to **36**, the product diastereomers (dr 92:8) could be separated by careful chromatography. Data for characterization of the major product **41**: $[\alpha]_D^{20}$ +2.4 (c 0.83, $CHCl_3$). R_f = 0.63 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 2955, 2859, 1759, 1650, 1471, 1364, 1292, 1255, 1094, 954. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 5.83 (d, J = 1.4 Hz, 1H), 5.48 (s, 1H), 4.53 (ABq, $\Delta\nu_{AB}$ = 41 Hz, J_{AB} = 12.1 Hz, 2H), 3.67–3.62 (m, 3H), 3.45 (td, J = 9.8, 5.1 Hz, 1H), 2.52 (dd, J = 16.9, 1.7 Hz, 1H), 2.26–2.21 (m, 1H), 2.17 (d, J = 16.9 Hz, 1H), 2.00 (d, J = 1.4 Hz, 3H), 1.91–1.85 (m, 1H), 1.81–1.74 (m, 1H), 1.72–1.63 (m, 2H), 1.61–1.54 (m, 1H), 0.98 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 3H), 0.84 (d, J = 6.0 Hz, 3H), 0.03 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.5, 128.4, 127.8, 127.6, 126.2, 118.4, 90.4, 73.8, 72.3, 60.3, 50.6, 50.3, 40.8, 34.7, 29.5, 29.1, 26.0, 22.7, 22.0, 20.2, 18.3, 13.9, –5.2 (2C). HR-MS-ESI calcd for $C_{31}H_{48}O_4SiNa$ [M + Na^+]: 535.3220; found: 535.3247. Data for the complete characterization of the minor butenolide (*S*)-5-(benzyloxymethyl)-5-(((4*R*,5*R*)-5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-isopropyl-5-methylcyclopent-1-enyl)methyl)-4-methylfuran-2(5*H*)-one (**42**): $[\alpha]_D^{20}$ –22.3 (c 0.16, $CHCl_3$). R_f = 0.62 (hexanes/EtOAc, 2:1). IR

(film, cm^{-1}): 2955, 2859, 1759, 1650, 1471, 1364, 1292, 1255, 1094, 954. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.25 (m, 5H), 5.83 (s, 1H), 5.52 (s, 1H), 4.51 (ABq, $\Delta\nu_{AB}$ = 30 Hz, J_{AB} = 12.0 Hz, 2H), 3.67–3.60 (m, 3H), 3.39 (td, J = 9.8, 5.3 Hz, 1H), 2.40 (d, J = 16.6 Hz, 1H), 2.30–2.19 (m, 2H), 2.05 (d, J = 0.9 Hz, 3H), 1.91–1.87 (m, 1H), 1.80–1.74 (m, 1H), 1.71–1.61 (m, 2H), 1.59–1.52 (m, 1H), 0.98 (d, J = 5.9 Hz, 3H), 0.88–0.83 (m, 15H), 0.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.3, 170.2, 141.8, 137.5, 128.4, 127.8, 127.7, 126.0, 118.4, 90.5, 73.8, 72.0, 60.5, 50.7, 50.3, 40.9, 34.9, 29.5, 29.2, 26.0, 22.7, 22.2, 19.9, 18.3, 14.0, –5.2, –5.3. HR-MS-ESI calcd for $C_{31}H_{48}O_4SiNa$ [M + Na^+]: 535.3220; found: 535.3199.

*(**R**)-5-((Benzyloxy)methyl)-5-(((4**R**,5**R**)-5-(2-hydroxyethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl)-4-methylfuran-2(5**H**)-one (43)*

To a solution of **41** and **42** (49.4 mg, 96.3 μmol) and CH_3CN (1 mL) in a plastic vial was added aqueous HF (5.4 μL, 52% in H_2O, 0.579 mmol) and the mixture was stirred for 15 min. The reaction was poured into saturated aqueous $NaHCO_3$ (8 mL) and stirred for 5 min. EtOAc (6 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (2 × 8 mL) and the organic extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a clear light brown oil. The crude product was purified by flash column chromatography (hexanes/EtOAc, 1:1) to give **43** and **44** (34.8 mg, 91%) as a mixture of C_2 diastereomers (dr 60:40) as a clear colorless viscous oil. Separation of the C_2 diastereomers was by preparative HPLC; 30% EtOAc in hexanes 22 mL/min, loading in 19% CH_2Cl_2 in hexanes (three runs), afforded 21.3 mg of **43** (retention time (t_R): 32.772 min) and 10.8 mg of **44** (t_R: 39.079 min). Analytical data: 30% EtOAc in hexanes for **43** (t_R: 44.215 min), for **44** (t_R: 52.065 min). Characterization data for **43**: $[\alpha]_D^{20}$ –2.3 (*c* 1.15, $CHCl_3$). R_f = 0.14 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 3418, 2955, 1743, 1648, 1455, 1293, 1100, 957. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.25 (m, 5H), 5.83 (d, J = 1.4 Hz, 1H), 5.46 (s, 1H), 4.52 (ABq, $\Delta\nu_{AB}$ = 32 Hz, J_{AB} = 12.0 Hz, 2H), 3.72–3.61 (m, 1H), 3.65 (ABq, $\Delta\nu_{AB}$ = 26 Hz, J_{AB} = 10.1 Hz, 2H), 3.54–3.46 (m, 1H), 2.55 (d, J = 16.6 Hz, 1H), 2.30–2.16 (m, 2H), 2.03 (d, J = 1.4 Hz, 3H), 1.93–1.77 (m, 2H), 1.72–1.59 (m, 2H), 1.49–1.47 (m, 1H), 0.97 (d, J = 4.3 Hz, 3H), 0.87 (s, 3H), 0.84 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.4, 170.1, 142.0, 137.4, 128.5, 127.9, 127.7, 126.7, 118.4, 90.4, 73.8, 72.3, 59.8, 50.6, 50.2, 40.6, 34.8, 29.2, 29.1, 22.6, 21.9, 20.3, 13.9. HR-MS-ESI calcd for $C_{25}H_{34}O_4Na$ [M + Na^+]: 421.2355; found: 421.2343. Complete characterization of the minor butenolide (*S*)-5-((benzyloxy)methyl)-5-(((4*R*,5*R*)-5-(2-hydroxyethyl)-4-isopropyl-5-methylcyclopent-1-en-1-yl)methyl)-4-methylfuran-2(5*H*)-one (**44**): $[\alpha]_D^{20}$ –34.2 (*c* 0.70, $CHCl_3$). R_f = 0.14 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 3431, 2955, 2868, 1745, 1648, 1454, 1365, 1100. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.26 (m, 5H), 5.83 (s, 1H), 5.52 (s, 1H), 4.52 (ABq, $\Delta\nu_{AB}$ = 12.0 Hz, J_{AB} = 11.3 Hz, 2H), 3.72–3.50 (m, 4H), 2.52 (d, J = 15.9 Hz, 1H), 2.32–2.25 (m, 1H), 2.21 (d, J = 15.9 Hz, 1H), 2.08 (s, 3H), 1.96–1.55 (m, 5H), 1.00 (d, J = 6.1 Hz, 3H), 0.88–0.87 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.5, 171.1, 142.5, 137.4, 128.4, 127.9, 127.6, 127.2, 117.9, 90.2, 73.7, 71.5, 60.2, 50.6, 50.0, 40.7, 35.1, 29.9, 29.3, 22.4, 22.2, 20.2, 14.0. HR-MS-ESI calcd for $C_{25}H_{34}O_4Na$ [M + Na^+]: 421.2355; found: 421.2344.

*2-((1**R**,5**R**)-2-(((**R**)-2-((Benzyloxy)methyl)-3-methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl)-5-isopropyl-1-methylcyclopent-2-en-1-yl)acetaldehyde (49)*

A solution of alcohol **43** (40.8 mg, 0.102 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and was treated with $NaHCO_3$ (26 mg, 0.306 mmol) and Dess–Martin periodinane (56.4 mg, 0.133 mmol), and the cold bath was then removed. After 2 h, the reaction was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), diluted with CH_2Cl_2 (5 mL), and stirred for 20 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a clear colorless oil. The product was purified by flash column chromatography (hexanes/EtOAc, 4:1) to provide aldehyde **49** (37.3 mg, 92%) as a clear colorless oil. $[\alpha]_D^{20}$ –7.6 (*c* 0.25, $CHCl_3$). R_f = 0.46 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 2958, 2870, 1754, 1717, 1650, 1454, 1291, 1098, 954. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.71 (dd, J = 3.7, 2.1 Hz, 1H), 7.39–7.22 (m, 5H), 5.83 (d, J = 1.4 Hz, 1H), 5.58 (s, 1H), 4.51 (ABq, $\Delta\nu_{AB}$ = 25 Hz, J_{AB} = 12.0 Hz, 2H), 3.61 (ABq, $\Delta\nu_{AB}$ = 25 Hz, J_{AB} = 10.2 Hz, 2H), 2.61–2.52 (m, 2H), 2.44 (dd, J = 16.0, 2.1 Hz, 1H), 2.37–2.30 (m, 1H), 2.24 (d, J = 17.9 Hz, 1H), 2.16 (d, J = 1.4 Hz, 3H), 2.03–1.95 (m, 1H), 1.80–1.70 (m, 2H), 0.99 (s, 3H), 0.98 (d, J = 6.2 Hz, 3H), 0.86 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.7, 172.1, 170.0, 141.0, 137.3, 128.5, 128.1, 127.9, 127.7, 118.4, 90.1, 73.8, 71.8, 52.8, 51.5, 50.7, 34.7, 29.9, 29.1, 22.8, 21.7, 19.7, 13.9. HR-MS-ESI calcd for $C_{25}H_{32}O_4Na$ [M + Na^+]: 419.2198; found: 419.2183.

*(3a**S**,4**R**,5a**R**,6**R**,9a**R**)-9a-(Benzyloxymethyl)-4-hydroxy-6-isopropyl-3a,5a-dimethyl-3a,4,5,5a,6,7,9,9a-octahydroazuleno[5,6-**b**]furan-2(3**H**)-one (50a)*

To a solution of freshly prepared SmI_2 (9.2 mL, 0.1 mol/L in THF, 0.918 mmol) at rt was added HMPA (639 μL, 3.67 mmol) dropwise. After 2 min, aldehyde **49** (178 mg, 0.449 mmol) in a solution of THF/*t*-BuOH (46 mL, 100:1 by volume) was added dropwise over 7 min. The reaction quickly became a yellow color and an additional amount of SmI_2 (1.6 mL, 0.1 mol/L in THF, 0.16 mmol) was added to the reaction mixture via syringe. After 5 min, the reaction was quenched by the addition of silica gel (20 mL volume). The crude reaction mixture was filtered through a plug of silica gel using ethyl acetate. The organic layer was concentrated in vacuo to provide a clear yellow oil. The product was purified by flash column chromatography (hexanes / EtOAc, 4:1) to provide **50a** and **50b** (113 mg, 63%) as a 66:34 mixture of C_8 diastereomers. These diastereomers were separated by HPLC using a Supelco Ascentis Si column (hexanes / isopropyl alcohol, 98:2) to provide pure **50a** (73 mg; t_R: 40.2 min) and pure **50b** (36 mg; t_R: 33.6 min) as clear colorless oils. Characterization data for **50a**: $[\alpha]_D^{20}$ –20.3 (*c* 1.40, $CHCl_3$). R_f = 0.35 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 3479, 2955, 2870, 1771, 1454, 1418, 1236, 1103, 1070 953. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.27 (m, 5H), 5.34 (s, 1H), 4.53 (ABq, $\Delta\nu_{AB}$ = 8 Hz, J_{AB} = 12 Hz, 2H), 4.14–4.08 (m, 1H), 3.63 (ABq, $\Delta\nu_{AB}$ = 118 Hz, J_{AB} = 10.6 Hz, 2H), 3.11 (d, J =

18.1 Hz, 1H), 2.64 (d, J = 13.9 Hz, 1H), 2.62 (d, J = 18.1 Hz, 1H), 2.39 (d, J = 14.1 Hz, 1H), 2.29 (ddd, J = 16.2, 7.8, 2.6 Hz, 1H), 1.98–1.84 (m, 3H), 1.76–1.65 (m, 2H), 1.51 (dd, J = 18.1, 9.5 Hz, 1H), 1.15 (s, 3H), 1.01 (s, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 176.1, 144.2, 137.7, 128.4, 128.2, 127.6, 127.5, 88.6, 74.0, 73.7, 69.0, 60.4, 49.3, 48.2, 48.0, 42.3, 36.1, 33.4, 29.5, 22.8, 22.7, 20.1, 16.1. HR-MS-ESI calcd for $C_{25}H_{34}O_4Na$ [M + Na^+]: 421.2355; found: 421.2341. Complete characterization data for (3a*S*,4*S*,5a*R*,6*R*,9a*R*)-9a-((benzyloxy)methyl)-4-hydroxy-6-isopropyl-3a,5a-dimethyl-3a,4,5,5a,6,7,9,9a-octahydroazuleno[5,6-*b*]furan-2(3*H*)-one (**50b**): $[\alpha]_D^{20}$ –1.9 (*c* 0.7, $CHCl_3$). R_f = 0.35 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 3467, 2956, 2869, 1763, 1417, 1238, 1104, 1096, 956. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 5.45 (s, 1H), 4.56 (ABq, $\Delta\nu_{AB}$ = 29 Hz, J_{AB} = 11.8 Hz, 2H), 3.75 (d, J = 10.9 Hz, 1H), 3.74–3.71 (m, 1H), 3.57 (d, J = 10.8 Hz, 1H), 2.85 (d, J = 13.4 Hz, 1H), 2.76 (d, J = 17.3 Hz, 1H), 2.54 (d, J = 13.3 Hz, 1H), 2.49 (d, J = 17.3 Hz, 1H), 2.29 (ddd, J = 16.0, 7.7, 2.5 Hz, 1H), 2.01–1.89 (m, 3H), 1.81–1.69 (m, 1H), 1.63–1.58 (m, 2H), 1.18 (s, 3H), 1.01 (d, J = 6.5 Hz, 3H), 0.99 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H. ^{13}C NMR (126 MHz, $CDCl_3$) δ: 176.0, 144.6, 137.9, 128.4, 127.6, 127.4 (2C), 89.7, 75.3, 73.4, 72.4, 57.1, 49.0, 48.7, 45.1, 40.6, 35.9, 31.6, 29.6, 22.9, 22.8, 21.3, 21.1. HR-MS-ESI calcd for $C_{25}H_{34}O_4Na$ [M + Na^+]: 421.2355; found: 421.2343.

(3aR,5aR,6R,9aR)-9a-((Benzyloxy)methyl)-6-isopropyl-3a,5a-dimethyl-3,3a,5,5a,6,7,9,9a-octahydroazuleno[5,6-b]furan-2,4-dione (53)

To a solution containing a mixture of **50a** and **50b** (4.4 mg, 11 μmol) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (2.8 mg, 33 μmol) and Dess–Martin periodinane (14.6 mg, 14.3 μmol). The reaction was stirred for 50 min and was quenched with a solution of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). After 20 min, the layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 4 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated in vacuo to provide a clear colorless oil. Purification via flash chromatography (hexanes/EtOAc, 5:1) provided pure ketone **53** (3.4 mg, 77%) as a white crystalline solid (see Supplementary data). $[\alpha]_D^{20}$ +60.3 (*c* 1.22, $CHCl_3$). R_f = 0.62 (hexanes/EtOAc, 2:1). IR (film, cm^{-1}): 2960, 2870, 1783, 1697, 1497, 1454, 1378, 1233, 1117, 1068, 957. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.27 (m, 5H), 5.51 (bs, 1H), 4.55 (ABq, $\Delta\nu_{AB}$ = 11 Hz, J_{AB} = 11.7 Hz, 2H), 3.75 (ABq, $\Delta\nu_{AB}$ = 53 Hz, J_{AB} = 10.7 Hz, 2H), 3.13 (d, J = 17.8 Hz, 1H), 2.92 (d, J = 11.2 Hz, 1H), 2.76 (d, J = 14.2 Hz, 1H), 2.55 (d, J = 11.1 Hz, 1H), 2.45 (d, J = 17.8 Hz, 1H), 2.33 (ddd, J = 16.3, 7.9, 2.9 Hz, 1H), 2.22–2.14 (m, 1H), 1.99–1.87 (m, 1H), 1.79–1.66 (m, 1H), 1.57–1.48 (m, 1H), 1.40 (s, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.94 (s, 3H), 0.89 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 209.0, 174.0, 143.5, 137.4, 129.3, 128.4, 127.8, 127.7, 86.3, 73.9, 72.6, 59.6, 57.2, 52.3, 49.2, 39.8, 35.7, 35.5, 29.4, 22.7, 22.6, 20.5, 19.3, 18.5. HR-MS-ESI calcd for $C_{25}H_{32}O_4Na$ [M + Na^+]: 419.2198; found: 419.2186.

O-(3aS,4S,5aR,6R,9aR)-9a-(Benzyloxymethyl)-6-isopropyl-3a,5a-dimethyl-2-oxo-2,3,3a,4,5,5a,6,7,9,9a-decahydroazuleno[5,6-b]furan-4-yl 1H-imidazole-1-carbothioate (54)

To a solution of **50a** and **50b** (6.1 mg, 0.15 mmol) in THF (500 μL) was added 1,1′-thiocarbonyldiimidozole (5.5 mg, 0.031 mmol). The reaction was heated to 80 °C for 16 h. The reaction was cooled to rt, and the solvent was removed in vacuo and purified by flash column chromatography (hexanes/EtOAc, 5:1 → 2:1) to provide the imidazole-1-carbothioate (3.7 mg, 48%, 71% brsm) as a clear colorless oil, which gave diagnostic signals upon ^{1}H NMR spectroscopy. R_f = 0.5 (hexanes/EtOAc, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.33 (s, 1H), 7.58 (s, 1H), 7.42–7.27 (m, 5H), 7.07 (s, 1H), 5.68 (dd, J = 8.5, 1.7 Hz, 1H), 5.58 (s, 1H), 4.58 (ABq, $\Delta\nu_{AB}$ = 20 Hz, J_{AB} = 12.0 Hz, 2H), 3.73 (ABq, $\Delta\nu_{AB}$ = 57 Hz, J_{AB} = 10.8 Hz, 2H), 3.01 (d, J = 13.7 Hz, 1H), 2.90 (d, J = 17.3 Hz, 1H), 2.55 (d, J = 17.3 Hz, 1H), 2.43 (d, J = 13.5 Hz, 1H), 2.37–2.25 (m, 2H), 1.74–1.67 (m, 1H), 1.21 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H), 0.91 (s, 3H). LR-MS-ESI calcd. for $C_{29}H_{37}N_2O_4S$ [M + H^+]: 509.2; found: 509.3.

Additional purification of this crude material was not undertaken. A solution of the crude intermediate thione (3.7 mg, 7.2 μmol) in toluene (500 μL) was directly treated with *n*-Bu_3SnH (7.8 μL, 0.029 mmol) and 2,2′-azobisisobutyronitrile (AIBN; 1 mg, 6.1 μmol) and then heated to 100 °C. After 5 h, the reaction was cooled to ambient temperature. After 16 h, the reaction was concentrated and purified by flash column chromatography (hexanes/EtOAc, 5:1) to provide **54** (2 mg, 74%) as a clear colorless oil. R_f = 0.58 (hexanes/EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35–7.26 (m, 5H), 5.47 (s, 1H), 4.56 (ABq, $\Delta\nu_{AB}$ = 41.9 Hz, J_{AB} = 12.0 Hz, 2H), 3.62 (ABq, $\Delta\nu_{AB}$ = 16.7 Hz, J_{AB} = 10.8 Hz, 2H), 2.89 (d, J = 13.4 Hz, 1H), 2.72 (d, J = 17.3 Hz, 1H), 2.32 (d, J = 17.4 Hz, 1H), 2.32–2.26 (m, 1H), 2.16 (d, J = 13.3 Hz, 1H), 1.94–1.89 (m, 1H), 1.77–1.63 (m, 3H), 1.63–1.42 (m, 3H), 1.08 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H), 0.91 (s, 3H), 0.89 (d, J = 6.6 Hz, 3H). LR-MS-ESI calcd. for $C_{25}H_{35}O_3$ [M + H^+]: 383.3; found: 383.3.

Supplementary data

Supplementary data are available with the article through the journal Web site http://nrcresearchpress.com/doi/suppl/10.1139/v2012-088. CCDC 901299 contains the X-ray data in CIF format for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/products/csd/request (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk). X-ray crystallographic data for ketone **53** are available in Molecular Structure Center Report 09013 (Indiana University Molecular Structure Center).

Acknowledgements

We gratefully acknowledge the National Science Foundation (CHE-1055441) and Indiana University (Faculty Research Support Program) for generous support.

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(35) The ketone **53** ($C_{25}H_{32}O_4$) was isolated as colorless needles (from hexanes/EtOAc), monoclinic, $P2_1$, a = 10.6858(4) Å, b = 6.5912(3) Å, c = 15.6583(7) Å, β = 100.169(3) Å, V = 1085.52(8) Å^3. A single crystal was mounted and data collection was carried out at 150 K using Cu Kα radiation. Final residues were R_1 = 0.0421 and wR_2 = 0.0842 (F^2, all data). The structure was solved with direct methods and refined with full-matrix least squares/difference Fourier cycles. All nonhydrogen atoms were refined with anisotropic displacement parameters (see the Supplementary data).

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Solid-phase synthesis of *N*-(buta-2,3-dien-1-yl)amides by the Crabbé reaction

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Abstract: The Crabbé homologation of polymer-supported propargylamine with paraformaldehyde, CuI, and dicyclohexylamine in 1,4-dioxane at 100 °C, followed by cleavage with dilute trifluoroacetic acid, furnishes *N*-(buta-2,3-dien-1-yl)amides as isolable products. The *N*-acyltriazene linker on Merrifield resin serves simultaneously as a protecting group for the nucleophilic primary amine. The product diversity is achieved by altering the acyl chloride in the acylation of the triazene linker. In addition to being a new route to nitrogen-containing allenes, our solid-phase method enables immobilization of these reactive cumulated dienes for further synthetic operations.

Key words: allene, solid phase, Crabbé, homologation, propargylamine.

Résumé : La réaction d'homologation de Crabbé de la propargylamine fixée à un polymère, par du paraformaldéhyde, en présence de CuI et de dicyclohexylamine, dans le 1,4-dioxane, à 100 °C, suivie par un clivage à l'aide d'acide trifluoroacétique dilué, conduit à la formation de *N*-(buta-2,3-dién-1-yl)amides comme produits isolables. Le *N*-acyltriazène utilisé comme coupleur sur la résine de Merrifield agit simultanément comme groupe protecteur pour l'amine primaire nucléophile. La diversion des produits est obtenue en modifiant la nature du chlorure d'acyle utilisé dans l'acylation du coupleur triazène. En plus d'être une nouvelle voie vers des allènes contenant de l'azote, notre méthode en phase solide permet d'immobiliser ces dienes cumulés réactifs en vue d'opérations de synthèse ultérieures.

Mots-clés : allène, phase solide, Crabbé, homologation, propargylamine.

[Traduit par la Rédaction]

Introduction

Allenes as cumulated dienes are useful and versatile synthetic intermediates in numerous synthetic applications, e.g., in gold-catalyzed intramolecular hydroamination reactions[1] and in photoinduced [2 + 2] cycloadditions with olefins.[2] Moreover, nitrogen-containing, such as amidomethyl-substituted, allenes are useful building blocks in organic synthesis.[3] Certain aminoallenes, such as 1-amino-2,3-butadiene, have been associated with monoamine oxidase B inhibition.[4] Our continuing interest in immobilizing amines onto solid support and modifying them by carbon–carbon bond-forming reactions[5] was the starting point for the study of the one-carbon homologation of solid-supported propargylamine. Keeping in mind the easy nucleophilic attack of primary amines at the central carbon atom of allenes, to give enamines,[6] the general reactivity and potent lability of cumulated carbon–carbon double bonds make the synthesis and use of allenes sometimes challenging.

To the best of our knowledge, there are no reports about the solid-phase synthesis of allenes. Rafai Far and Tidwell[7] prepared allenecarboxylic esters for β-ketoester equivalents by the Wittig reaction, starting from α-haloacetates, which were attached on soluble poly(ethylene glycol). On the other hand, Ma et al.[8,9] used 1,2-allenyl carboxylic acids in solution in a palladium(0)-catalyzed cyclization reaction with polymer-bound aryl iodides to give butenolides. The α-allenyl amine derivatives of our interest have previously been synthesized in solution, e.g., Casara et al.[10] prepared a series of α-allenyl amines from *N-tert*-butoxycarbonyl-protected propargylamines by the Crabbé reaction for inhibition studies of pyridoxal-phosphate-dependent enzymes. There are, however, no examples of the synthesis of simple *N*-(buta-2,3-dien-1-yl) amides in the literature.

Owing to the sensitivity of these nitrogen-containing allenes, the linker on the polymer must be stable enough during the preparation and storage to serve simultaneously as the crucial protective group. In addition, the cleavage step should be

Received 29 June 2012. Accepted 27 September 2012. Published at www.nrcresearchpress.com/cjc on 19 December 2012.

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This article is part of a Special Issue dedicated to Professor Derrick Clive.

performed fast and simply, under as mild conditions as possible. The drawbacks of many cleavage procedures of amines are long reaction times under relatively harsh conditions, such as 60% trifluoroacetic acid (TFA) in dichloromethane[11] or oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[12] These procedures would not be among the first desirable options to choose. It would also be preferable if the allenes could be cleaved as some less reactive derivatives of amines.

We decided to test the triazene linkage[13] for immobilization of propargylamine to fit the requirements mentioned previously. This linker is prepared from Merrifield resin-bound 3-aminophenol by diazotization and adding a primary amine to the polymer-bound diazonium salt. The triazene moiety can be acylated with acyl chlorides and it is cleavable as an amide, with 5% TFA in CH_2Cl_2 at room temperature, within a few minutes. These immobilized triazenes are remarkably stable at room temperature under dry conditions and they are safe to handle when compared with triazenes in solution, which are potent carcinogens.[14]

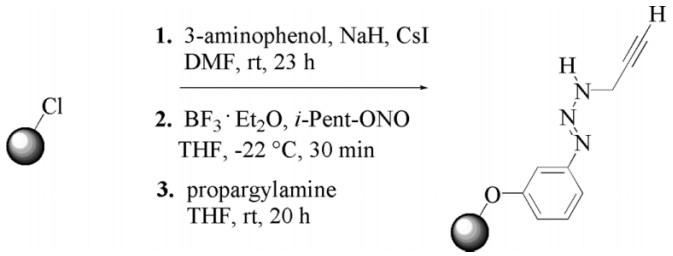
For the allene formation we used the Crabbé reaction,[15] which is a powerful method for homologation of terminal alkynes. In the updated procedure, alkyne is heated with paraformaldehyde, dicyclohexylamine, and copper(I) iodide in 1,4-dioxane at 100 °C.[16] Since the reaction involves a Mannich base derived from acetylene, formaldehyde, and amine as an intermediate, which turns to the allene via the copper-mediated 1,5-hydride transfer, the use of a secondary amine is necessary.[15,17] Anhydrous conditions are essential. In comparison, in a study by Bieber and da Silva,[18] a series of terminal alkynes was subjected to the related Mannich conditions in aqueous dimethyl sulfoxide at 30 °C to give tertiary propargylamines as products instead of allenes.

Results and discussion

We immobilized propargylamine on Merrifield resin (Scheme 1) according to the known literature procedure for primary amines,[13] with minor modifications. In the attachment of 3-aminophenol to the Merrifield resin, 5 mol % of cesium iodide was added to increase the rate of the substitution reaction. For the formation of diazonium salt from polymer-bound 3-aminophenol, isopentyl nitrite was used instead of *tert*-butyl nitrite. This three-step transformation was a reliable method and easy to reproduce. The intermediate orange (deep carmine-red with solvent) polymer-bound diazonium salt is relatively stable to air and safe to handle. The air-stable brown-orange (deep orange-red with solvent) propargyltriazene resin is formed by the addition of propargylamine to the polymer-bound diazonium salt in dry tetrahydrofuran (THF) at room temperature.

To broaden the product diversity and to improve the stability, the NH group of the triazene moiety was acylated with various acyl chlorides[13] prior to the Crabbé reaction and cleavage (Scheme 2). At this stage, the order of introduction of the reagents into the reaction medium is particularly important. Triethylamine must be added before the acyl chloride to maintain a basic solution phase throughout the reaction. Acyl chlorides alone cleave the extremely acid-labile triazene,[19] liberating propargylamine as an amide into the solution. In fact, we observed that the triazene linker is cleaved by far more dilute TFA concentrations than 5% in CH_2Cl_2, so acidic contamination must be excluded in all operations.

Scheme 1. Loading of propargylamine to polystyrene through a triazene linker. rt, room temperature.



In our studies with seven various polymer-bound acyltriazenes, the yield of allene from propargyl triazene resin varied between 10% and 63%, depending on the N substituent (Table 1). It is very likely that the allene formation is strongly controlled by steric factors, because the best yields were obtained with simple small-sized aliphatic N substituents, acetyl, and pivaloyl groups. Otherwise, a yield significantly higher than 11% of the electronically very similar *N*-octanoyl-substituted product would have been expected. However, although sterically crowded, the pivaloyl group is apparently too short to reach the vicinity of the terminal acetylene unit to interfere with the reaction. On the other hand, the reactivity of the acryloyl group apparently suppresses the yield, despite its small size.

It must be pointed out that the yield of the isolated product does not necessarily solely illustrate the success of the Crabbé reaction on resin. Decomposition after the cleavage cannot be excluded, despite the fast procedure (2 × 15 min) and the immediate neutralization of additional TFA using $NaHCO_3$, after filtering the resin off. This was very evident with the *N*-2-phenylacetyl-substituted triazene resin, which gave, according to ^{1}H NMR, an approximate 1:1 mixture of the desired allene and phenylacetic acid as the cleavage product. Decomposition, although in this particular case probably independent of the allene moiety, is understandable considering the easy acidolysis of 2-phenylacetamide to phenylacetic acid.[20] According to thin-layer chromatography, this allene product also decomposes on silica gel.

We studied the stability of the isolated and purified *N*-4-nitrobenzoyl-substituted allene by dissolving a sample to 5% TFA in $CDCl_3$ and monitoring the content by ^{1}H NMR for 24 h (27 °C, 8 h; and 21 °C, 16 h). A little surprisingly, the product was totally intact despite this prolonged acidic treatment, demonstrating its stability in mild acidic conditions. Thus, we assume that the cleavage with 5% TFA in CH_2Cl_2 is not the origin of decomposition or suppression of the yields, except with the previously mentioned *N*-2-phenylacetyl derivative.

The *N*-(buta-2,3-dien-1-yl)amides generally appeared to be fairly stable when stored below –18 °C under argon and protected from light. The compounds could be characterized unambiguously with very distinct allenic traces at 1950–1960 cm^{-1} by FT-IR, and 4.7–4.9 ppm (td) and 5.1–5.4 ppm (quint) by ^{1}H NMR. The CH_2, CH, and central carbon atom signals were also distinct at 78, 87–88, and 208 ppm, respectively, by ^{13}C NMR. However, a small amount of aliphatic polymers appeared in most products, according to signals in the ^{1}H and ^{13}C NMR, at around 0.8–2.2 and 20–30 ppm, respectively, demonstrating slow decomposition. Despite this, considering the treatment of the previously mentioned *N*-phenylacetyl derivative,

Scheme 2. *N*-Acylation and the allene formation from the propargyltriazene resin. rt, room temperature.

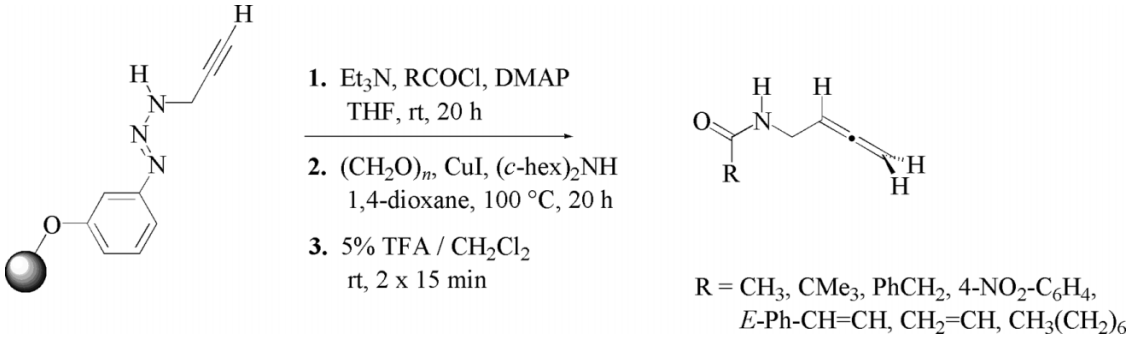


Table 1. Yields of isolated *N*-(buta-2,3-dien-1-yl)amides obtained with various acyl chlorides.

Entry	R in RCOCl	Yield (%)
1	CH_3	63
2	CMe_3	53
3	$PhCH_2$	10
4	4-NO_2–C_6H_4	13
5	(*E*)-Ph–CH=CH	20
6	CH_2=CH	18
7	$CH_3(CH_2)_6$	11

upon isolation (see the Experimental section) it is evident that these allenes can tolerate even water for short periods.

Conclusion

We have developed a solid-phase method that introduces new possibilities in the syntheses of biologically active nitrogen-containing allenes. All reagents required in our reaction sequence are inexpensive and the final products are afforded by a cleavage reaction under very mild conditions. Although the yields of the isolated products in this preliminary study are moderate, our method enables access to *N*-(buta-2,3-dien-1-yl)amides, demonstrated by seven new characterized compounds. Owing to the versatility of allenes as synthetic intermediates, the possibility of immobilizing potentially labile cumulated carbon–carbon double bonds on solid support for further reactions is even more interesting. Hence, our solid-phase method introduces interesting possibilities for new applications.

Experimental

General

Reagents were obtained from Sigma-Aldrich, Fluka, Acros, Riedel-de Haën, and Merck. Merrifield resin (loading: 0.64 mmol/g, 200–400 mesh, cross-linked with 1% divinylbenzene) was commercially available from Novabiochem. The yields are based on the actual loading of 0.59 mmol/g of the propargyltriazene resin. *N*,*N*-Dimethylformamide (DMF) was dried by distillation from anhydrous $CaSO_4$ under reduced pressure. THF and 1,4-dioxane were dried by distillation from sodium or with activated 3 Å molecular sieves. Triethylamine was dried by distillation from P_2O_5 or with activated 3 Å molecular sieves. Dicyclohexylamine was dried with activated 3 Å molecular sieves. Otherwise, commercial grade reagents and solvents were used without further purification or drying. Merck aluminium sheets coated with silica gel 60 F_{254} were used for thin-layer chromatography and they were visualized by UV light at 254 nm or by brief heating at 120 °C, after wetting with 0.4 mol/L vanilline solution in H_2SO_4/ethanol (1:100, v/v). Column chromatography was performed with Fluka silica gel 60, 230–400 mesh. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Varian Mercury 300 Plus spectrometer. Chemical shifts are relative to the residual solvent signal 7.26 ppm of $CDCl_3$ in the ^1H spectra and to the NMR solvent signal 77.2 ppm for $CDCl_3$ in the ^{13}C spectra. FT-IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer equipped with a one reflection attenuated total reflection (ATR) unit. Melting points were obtained with an Electrothermal melting point apparatus (Cat. No. IA6301) and they are uncorrected. High-resolution (HR) electron impact (EI) mass spectrometry (MS) analyses were performed using a Jeol JMS-700 mass spectrometer at 700 eV.[21] GC–MS analyses were performed using an Agilent 6890N gas chromatograph equipped with a DB-1MS capillary column (34.0 m × 250 μm × 0.25 μm; calibrated) and Agilent 5973 Network mass-selective detector.

Loading of propargylamine to polystyrene through a triazene linker

Dry DMF (13 mL/g resin) was added to a mixture of the Merrifield resin (loading: 0.64 mmol/g), sodium hydride as a dispersion with mineral oil (~50%, 5 equiv), and cesium iodide (0.05 equiv) under argon. 3-Aminophenol (5 equiv) in dry DMF (4 mL/g) was slowly added at 0 °C and the mixture was stirred at room temperature for 23 h. The resin was filtered, washed three times (3 × 3 mL/g resin) with each of THF, MeOH, and CH_2Cl_2, and dried fast in high vacuum. Dry THF (9 mL/g resin) was added and the mixture was cooled under argon to –22 °C by means of EtOH / dry ice. After that, BF_3·Et_2O (8 equiv) was added, followed after 5 min by isopentyl nitrite (8 equiv). The mixture was stirred for 30 min in an EtOH / dry ice bath, filtered, and washed four times (4 × 3 mL/g resin) with cold THF. Dry THF (9 mL/g resin) and propargylamine (10 equiv) were added and the mixture was stirred at room temperature for 20 h under argon. After the addition of methanol/THF (1:1, v/v; 3 mL/g resin), the mixture was filtered, washed three times (3 mL/g resin) with each of THF, MeOH, and CH_2Cl_2, and dried in vacuo to constant

weight, which is in agreement with the quantitative attachment of propargylamine, with a new loading of 0.59 mmol/g. The resin was stored in a desiccator at room temperature.

General procedure for the *N*-acylation and the allene formation from the propargyltriazene resin

Propargyltriazene resin (1.0 g, 0.59 mmol/g) was swollen in 10 mL of dry THF. A catalytic amount of 4-dimethylaminopyridine (DMAP) and 1.0 mL of dry triethylamine were added, followed by 5–7 equiv of the acyl chloride under stirring. The mixture was stirred at room temperature for 21–24 h. The resin was filtered and washed twice (2 × 10 mL) with each of DMF, MeOH, THF, diethyl ether, and CH_2Cl_2, and introduced directly into the allene formation reaction. The resin, 5–6 equiv of paraformaldehyde, 0.5–0.6 equiv of CuI, and 2 equiv of dicyclohexylamine, in 5.0–10 mL of dry 1,4-dioxane, were stirred under argon at 100 °C for 20–22 h. The resin was filtered, washed twice (2 × 10 mL) with each of 1,4-dioxane, *n*-hexane, THF, diethyl ether, and CH_2Cl_2, and subjected to the cleavage step.

General procedure for the cleavage of the *N*-acylated allene product

The polymer-bound *N*-acylated allene product was double-cleaved by stirring the resin twice in 5% trifluoroacetic acid in dichloromethane (10 mL) at room temperature for 15 min. After both treatments, the resin was filtered and washed (1 × 10 mL) with each of CH_2Cl_2, diethyl ether, and CH_2Cl_2. The filtrates were immediately neutralized with solid $NaHCO_3$ (2.0 g), and the solvents were evaporated. The allene product was purified by flash chromatography if necessary or applicable and stored in a freezer, under argon and protected from light.

Syntheses of *N*-(buta-2,3-dien-1-yl)amides (1–7)

^{1}H NMR and ^{13}C NMR spectra for compounds **1–7** are available in the Supplementary data.

N-*(Buta-2,3-dien-1-yl)acetamide (1)*

Propargyltriazene resin (1.0 g, 0.59 mmol) was treated with acetyl chloride (0.30 mL, 330 mg, 4.2 mmol) for 22 h according to the general procedure (without DMAP). The allene formation was achieved by reaction with paraformaldehyde (95.0 mg, 3.16 mmol CH_2O), CuI (59.2 mg, 0.311 mmol), and dicyclohexylamine (226 mg, 1.25 mmol) for 20 h. The product was cleaved (general procedure) and dried in vacuo. Yellow-brown oil (41.0 mg, 63%). R_f = 0.07 (EtOAc–*n*-hexane, 1:1/vanilline–H_2SO_4). IR (ATR, cm^{-1}): 705, 798, 849, 1152, 1548, 1647, 1959. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 3.86 (m, 2H), 4.87 (td, J = 3.3, 6.5 Hz, 2H), 5.21 (quint, J = 6.3 Hz, 1H), 6.05 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.8, 38.1, 78.2, 87.3, 172.2, 208.2. GC–MS (*m*/*z*): 111, 110, 72, 70, 69, 68, 43, 32, 30, 28 (100%), 18.

N-*(Buta-2,3-dien-1-yl)pivalamide (2)*

Propargyltriazene resin (1.0 g, 0.59 mmol) was treated with pivaloyl chloride (0.50 mL, 490 mg, 4.1 mmol) for 21 h according to the general procedure. The allene formation was achieved by reaction with paraformaldehyde (99.2 mg, 3.30 mmol CH_2O), CuI (56.4 mg, 0.296 mmol), and dicyclohexylamine (221 mg, 1.22 mmol) for 20 h. The product was cleaved (general procedure) and dried in vacuo. Yellow-brown oil (48.0 mg, 53%). R_f = 0.41 (EtOAc–*n*-hexane, 1:1/vanilline–H_2SO_4). IR (ATR, cm^{-1}): 705, 845, 1166, 1201, 1525, 1641, 1959, 2963, 3342. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (s, 9H), 3.84 (m, 2H), 4.88 (td, J = 3.5, 6.9 Hz, 2H), 5.24 (quint, J = 6.0 Hz, 1H), 6.05 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.6, 37.4, 38.9, 78.2, 88.2, 179.1, 207.9. HR-MS calcd for $C_9H_{15}NO$: 153.11536; found: 153.1146.

N-*(Buta-2,3-dien-1-yl)-2-phenylacetamide (3)*

Propargyltriazene resin (1.0 g, 0.59 mmol) was treated with phenylacetyl chloride (0.50 mL, 580 mg, 3.8 mmol) for 24 h according to the general procedure. The allene formation was achieved by reaction with paraformaldehyde (106 mg, 3.53 mmol CH_2O), CuI (64.3 mg, 0.338 mmol), and dicyclohexylamine (213 mg, 1.17 mmol) for 23 h. The product was cleaved (general procedure) and dried in vacuo. The oily residue was dissolved in chloroform, ~1 mL of triethylamine was added (removal of phenylacetic acid), the solution was filtered through a small plug of $NaHCO_3$, and the solvents were evaporated. The residue was dissolved in chloroform and ethyl acetate and washed twice with water. The organic phase was evaporated twice with acetone, and the product was dried in vacuo. Brown oil (11.4 mg, 10%). R_f = 0.0 (dec.; EtOAc–*n*-hexane, 1:1/UV). IR (ATR, cm^{-1}): 696, 719, 847, 1539, 1647, 1957, 2929. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.59 (s, 2H), 3.80 (m, 2H), 4.73 (td, J = 3.4, 6.8 Hz, 2H), 5.15 (quint, J = 6.1 Hz, 1H), 5.52 (br s, 1H), 7.22–7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.4, 43.9, 78.1, 88.0, 127.6, 129.2, 129.8, 134.8, 171.1, 207.7. HR-MS calcd for $C_{12}H_{13}NO$: 187.09971; found: 187.0990.

N-*(Buta-2,3-dien-1-yl)-4-nitrobenzamide (4)*

Propargyltriazene resin (1.0 g, 0.59 mmol) was treated with 4-nitrobenzoyl chloride (659 mg, 3.55 mmol) for 24 h according to the general procedure. The allene formation was achieved by reaction with paraformaldehyde (89.5 mg, 2.98 mmol CH_2O), CuI (60.2 mg, 0.316 mmol), and dicyclohexylamine (218 mg, 1.20 mmol) for 21 h. The product was cleaved (general procedure) and dried in vacuo. Column chromatography on SiO_2 (acetone–$CHCl_3$, 1:10) gave the product. Yellow crystals (17.1 mg, 13%; $CHCl_3$), mp 119–122 °C. R_f = 0.36 (EtOAc–*n*-hexane, 1:1/UV). IR (ATR, cm^{-1}): 686, 707, 861, 1349, 1510, 1598, 1638, 1955, 3287, 3329. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.07 (m, 2H), 4.92 (td, J = 3.4, 6.7 Hz, 2H), 5.35 (quint, J = 6.2 Hz, 1H), 6.38 (br s, 1H), 7.93 (d, J = 8.9 Hz, 2H), 8.28 (d, J = 8.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.2, 78.4, 87.8, 124.0, 128.3, 140.2, 149.8, 165.4, 208.2. HR-MS calcd for $C_{11}H_{10}N_2O_3$: 218.06914; found: 218.0704.

N-*(Buta-2,3-dien-1-yl)cinnamamide (5)*

Propargyltriazene resin (1.0 g, 0.59 mmol) was treated with cinnamoyl chloride (predominantly *E* isomer; 605 mg, 3.63 mmol) for 24 h according to the general procedure. The allene formation was achieved by reaction with paraformaldehyde (100 mg, 3.33 mmol CH_2O), CuI (67.5 mg, 0.354 mmol), and dicyclohexylamine (223 mg, 1.23 mmol) for 22 h. The product was cleaved (general procedure) and dried in vacuo. Column chromatography on SiO_2 (*n*-hexane to EtOAc–*n*-hexane, 2:3) gave the product. Pale yellow solid (23.0 mg, 20%; $CHCl_3$), mp 70–71 °C. R_f = 0.33 (EtOAc–*n*-hexane, 1:1/UV). IR (ATR, cm^{-1}): 674, 727, 853, 971, 1222, 1343,

1552, 1610, 1655, 1952, 3246. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.99 (m, 2H), 4.86 (td, J = 3.3, 6.5 Hz, 2H), 5.28 (quint, J = 6.3 Hz, 1H), 6.01 (br s, 1H), 6.43 (d, J = 15.6 Hz, 1H), 7.29–7.39 (m, 3H), 7.44–7.53 (m, 2H), 7.63 (d, J = 15.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.9, 77.8, 88.0, 120.6, 127.9, 128.9, 129.8, 134.9, 141.3, 165.9, 208.2. HR-MS calcd for $C_{13}H_{13}NO$: 199.09971; found: 199.0994.

N-*(Buta-2,3-dien-1-yl)acrylamide (6)*

Propargyltriazene resin (1.0 g, 0.59 mmol) was treated with acryloyl chloride (0.30 mL, 330 mg, 3.6 mmol) for 23 h according to the general procedure. The allene formation was achieved by reaction with paraformaldehyde (112 mg, 3.73 mmol CH_2O), CuI (57.8 mg, 0.303 mmol), and dicyclohexylamine (222 mg, 1.22 mmol) for 21 h. The product was cleaved (general procedure) and dried in vacuo. Column chromatography on SiO_2 (*n*-pentane to acetone–*n*-pentane, 1:4) gave the product. Pale yellow oil (13.0 mg, 18%). R_f = 0.20 (EtOAc–*n*-hexane, 1:1/vanilline–H_2SO_4). IR (ATR, cm^{-1}): 720, 730, 1240, 1463, 1660, 1739, 1958, 2849, 2917. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.94 (m, 2H), 4.86 (td, J = 3.4, 6.7 Hz, 2H), 5.26 (quint, J = 6.3 Hz, 1H), 5.65 (dd, J = 1.4, 10.2 Hz, 1H), 5.66 (br s, 1H), 6.09 (dd, J = 10.1, 17.1 Hz, 1H), 6.29 (dd, J = 1.4, 16.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.9, 78.1, 87.5, 127.5, 130.4, 166.4, 208.2. GC–MS (*m*/*z*): 123, 122, 94, 84, 70, 69, 55 (100%), 32, 28, 18.

N-*(Buta-2,3-dien-1-yl)octanamide (7)*

Propargyltriazene resin (1.0 g, 0.59 mmol) was treated with *n*-octanoyl chloride (0.50 mL, 480 mg, 3.0 mmol) for 17 h according to the general procedure. The allene formation was achieved by reaction with paraformaldehyde (95.0 mg, 3.16 mmol CH_2O), CuI (56.9 mg, 0.299 mmol), and dicyclohexylamine (216 mg, 1.19 mmol) for 22 h. The product was cleaved (general procedure) and dried in vacuo. Column chromatography on SiO_2 (*n*-hexane to EtOAc–*n*-hexane, 1:1) gave the product. Yellow oil (13.0 mg, 11%). R_f = 0.33 (EtOAc–*n*-hexane, 1:1/vanilline–H_2SO_4). IR (ATR, cm^{-1}): 843, 1544, 1644, 1959, 2925, 3286. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 6.9 Hz, 3H), 1.15–1.39 (m, 8H), 1.52–1.72 (m, 2H), 2.17 (t, J = 7.6 Hz, 2H), 3.85 (m, 2H), 4.84 (td, J = 3.4, 6.7 Hz, 2H), 5.22 (quint, J = 6.3 Hz, 1H), 5.57 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 22.7, 25.9, 29.2, 29.4, 31.8, 36.9, 37.5, 77.8, 88.3, 173.1, 208.1. HR-MS calcd for $C_{12}H_{21}NO$: 195.16231; found: 195.1628.

Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR spectra for compounds **1**–**7**) are available with this article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0255.

Acknowledgement

This research has been financially supported by TEKES (the Finnish Funding Agency for Technology and Innovation), Juvantia Pharma Ltd., Orion Corporation, Hormos Medical, the Academy of Finland, Drug Discovery and Development Technology Center (DDTC) research programme of the University of Helsinki, and the Finnish Work Environment Fund. We thank Dr. A.W.T. King for reviewing the language.

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(21) HR-MS analysis was preferred over elemental analysis for these relatively labile allenes. Our attempts to obtain HR-MS spectra of the acetyl- and acryloyl-substituted products (Table 1, entries 1 and 6) failed because of their high volatility in the prevacuum of the mass spectrometer. However, GC–MS and ^{1}H and ^{13}C NMR data are fully unambiguous with the structures shown.

One-pot synthesis of dihydrobenzisoxazoles from hydroxylamines, acetylenedicarboxylates, and arynes via in situ generation of nitrones

Pan Li, Chunrui Wu, Jingjing Zhao, Yang Li, Weichao Xue, and Feng Shi

Abstract: Aryne [3 + 2] cycloaddition with nitrones generated in situ from the addition of hydroxylamines to acetylenedicarboxylates affords moderate to good yields of dihydrobenzisoxazoles. This reaction extends the current scope of aryne cycloaddition to include in situ generated nitrones and produces functionalized dihydrobenzisoxazoles with a quaternary center.

Key words: nitrone, aryne, dipolar cycloaddition, reactive intermediate, dihydrobenzisoxazole.

Résumé : La cycloaddition [3 + 2] d'aryne à des nitrones générées in situ par l'addition d'hydroxylamines à des acétylènecarboxylates conduit à la formation avec des rendements allant de modérés à bons de dihydrobenzisoxazoles. Cette réaction prolonge la plage d'application des réactions de cycloadditions à des arynes de façon à inclure des nitrones générées in situ et à produire des dihydrobenzisoxazoles fonctionnalisés avec un centre quaternaire.

Mots-clés : nitrone, aryne, cycloaddition dipolaire, intermédiaire réactif, dihydrobenzisoxazole.

[Traduit par la Rédaction]

Introduction

In recent years, the [3 + 2] dipolar cycloaddition of arynes with various 1,3-dipoles has become resurgent[1–7] with the development of the Kobayashi aryne precursor,[8] 2-(trimethylsilyl)aryl triflates. Among the stable and isolable dipoles, diazo compounds[2] and azides[3] have received heavy investigation. However, another equally stable and isolable 1,3-dipole, nitrone, has not been thoroughly studied.

Nitrone cycloaddition with arynes affords dihydrobenzisoxazole derivatives, which are known synthetic intermediates and exhibit antimicrobial activities.[9] Because of the limited availability and few synthetic routes, the bioactivity of dihydrobenzisoxazole derivatives remains underinvestigated. It is thus not hard to envisage that aryne cycloaddition would represent a useful synthetic route for dihydrobenzisoxazoles and potentially allow for the construction of libraries around this privileged scaffold, given the relatively easy access to nitrones from readily available starting materials.[10]

Curiously, the investigation of aryne–nitrone cycloaddition has paid little attention to the scope of nitrones, but significant attention to the scope of arynes. In fact, almost every precursor of aryne has been studied in the context of cycloaddition with nitrones, including 1-aminobenzotriazoles (with $Pb(OAc)_4$),[11] 2-halophenyl triflates (with BuLi),[12] diazotized anthranilic acid,[13] benzoxadisilole derivatives (with $PhI(OAc)_2$ then fluoride),[14] and the Kobayashi precursor (with fluoride).[15] However, in most reports, only one or two nitrones were examined. The substitution pattern and functional group compatibility have been poorly explored. To the best of our knowledge, to date, only three reports have focused on the structural modification of nitrones,[12b,15] and regretfully only one has employed nitrones equipped with functional groups.[15a]

This deficiency can be partially ascribed to the fact that nitrones can be hard to work with. Conventional column chromatography is difficult to use with functionalized nitrones because of the high polarity they possess. Thus, to expand the scope of nitrones in the cycloaddition with arynes, alternative protocols have to be sought. In one attempt, Kivrak and Larock[16] employed oxaziridines in the aryne cycloaddition, which possibly act as a nitrone precursor. However, this strategy is largely limited to *N-tert*-butyl oxaziridines. We hypothesized that in situ generation of nitrones would solve the concerning issue of their isolation and purification, and hence accommodate complex structures and functional groups. The same strategy has been used by us and others in the cycloaddition of arynes with other dipoles,[17] but not yet with nitrones.

Hydroxylamine (**2**)[18] is the usual starting material for the preparation of nitrones. Although the most widely used route involves condensation with carbonyl compounds, electron-poor alkynes[19] (**1**), such as dimethyl acetylenedicarboxylate (DMAD), and allenes[20] have also been used to afford nitrones (**3**) via a Michael addition–tautomerization process (Scheme 1).

Received 3 May 2012. Accepted 23 October 2012. Published at www.nrcresearchpress.com/cjc on 18 December 2012.

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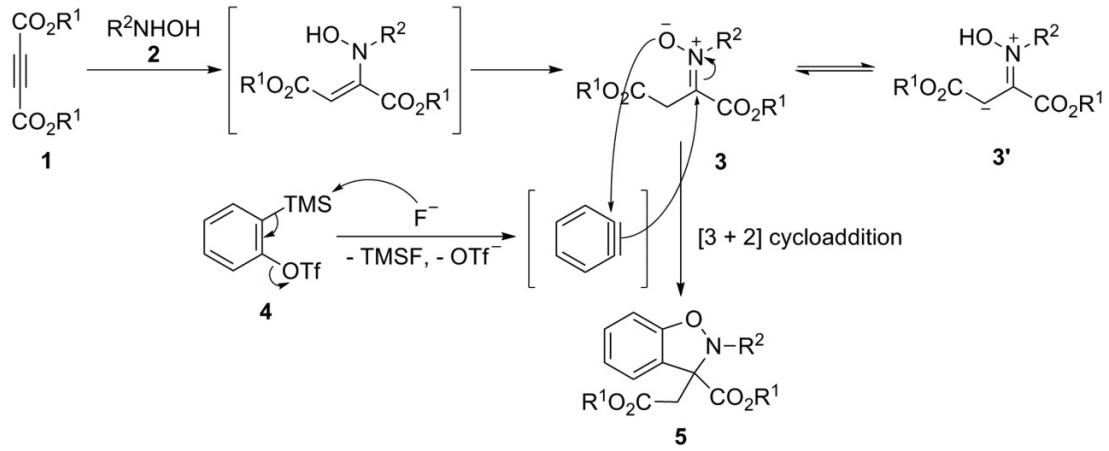
This article is part of a Special Issue dedicated to Professor Derrick Clive.

Scheme 1. Generation of nitrones from hydroxylamines and acetylenedicarboxylates.



Therefore, the treatment of a mixture of hydroxylamines and electron-poor alkynes with the Kobayashi aryne precursor in the presence of a fluoride source would lead to the in situ generation of both nitrones and arynes, and allow for a subsequent cycloaddition in a one-pot, three-component manner.[21]

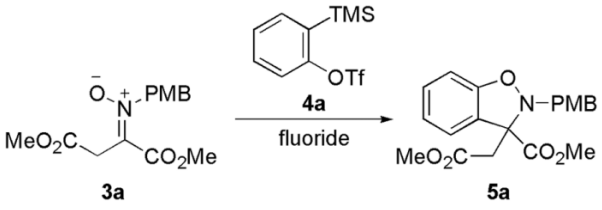
Results and discussion

We first isolated nitrone **3a** from the reaction of DMAD (**1a**) with *N*-(4-methoxybenzyl)hydroxylamine (**2a**) and subjected it to different reaction conditions with benzyne precursor **4a** (Table 1). Both CsF (Table 1, entry 1) and tetrabutylammonium fluoride (TBAF; Table 1, entries 4 and 5) proved effective fluoride sources, and the optimal conditions involved MeCN as the solvent at a slightly elevated temperature of 50 °C (Table 1, entry 1). The yield of this reaction was only moderate, despite a fairly clean thin-layer chromatography (TLC). The lost mass is mostly ascribed to some unidentifiable polar side products at the baseline of the TLC, and charging more benzyne precursor failed to provide a higher yield. The structure of **5a** was characterized by extensive NMR techniques, including heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC; see the Supplementary data). Note that nitrone **3a** contains an active methylene group, which may tautomerize to **3′** (Scheme 1) and react with arynes in a known σ-bond cleavage process.[22] This side product was not isolated, indicating that **3** reacted largely as the nitrone tautomer.

Next, we moved to the one-pot reaction conditions. We were pleased to find that the nitrone formation was very fast. As long as CsF (or TBAF) was added last, by the time we weighed out CsF (or withdrew TBAF solution from the bottle) the reaction between **1a** and **2a** was complete at room temperature (rt). This is an important observation as it may largely eliminate the potential cycloaddition of **3** with **1** as well as the *N*- or *O*-arylation of **2** with arynes. Under these conditions, **5a** was still isolated in a 58% yield (Table 2, entry 1), indicating no apparent loss of yield in the one-pot, three-component protocol. In addition, microwave irradiation afforded a 64% yield of the desired product.

We then started to examine the scope and limitation of this protocol (Table 2). First, different arynes were tested (Table 2, entries 2 and 3). The symmetrical dimethoxybenzyne afforded

Table 1. Reaction optimization.



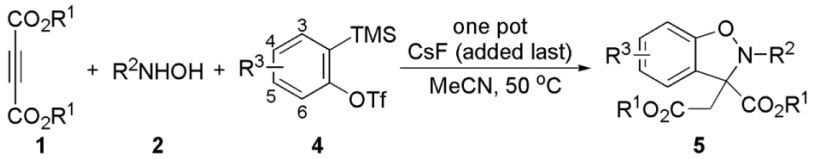
Entry	Fluoride	Solvent	*T* (°C)	Time (h)	Yield (%)[a]
1	CsF	MeCN	50	3	64
2	CsF	MeCN	rt	16	29
3	CsF	THF	70	16	9
4	TBAF	MeCN	rt	16	40
5	TBAF	THF	rt	16	46

Note: All reactions were carried out on a 0.4 mmol scale in 4 mL of solvent. **3a/4a**/fluoride = 1:1.2:2. rt, room temperature; THF, tetrahydrofuran; TBAF, tetrabutylammonium fluoride; PMB, *p*-methoxybenzyl; TMS, trimethylsilyl; Tf, trifluoromethanesulfonyl.

[a]Isolated yields.

the desired product **5b** in a moderate 46% yield (Table 2, entry 2), and the unsymmetrical 3-methoxybenzyne gave a single regioisomer in a 40% yield (Table 2, entry 3). This regioselectivity was similarly observed by Suzuki and co-workers[12a] and Larock and co-workers[15a] in their earlier studies. A range of hydroxylamines were examined next. As can be seen, hydroxylamines derived from aromatic aldehydes (Table 2, entries 4 and 5), an aromatic ketone (Table 2, entry 7), aliphatic aldehydes (Table 2, entries 8 and 9), and an aliphatic ketone (Table 2, entry 10) all afforded moderate to good yields of the corresponding products. Halogen, ether, and ester functional groups were well-tolerated. However, we noticed that the hydroxylamine derived from 4-cyanobenzaldehyde (**2d**) only afforded a complex mixture (Table 2, entry 6). Detailed study revealed that this nitrone was unstable under the reaction conditions and quickly decomposed upon exposure to CsF. Lastly, the replacement of DMAD with its analogues was also partly successful, as diethyl acetylenedicarboxylate (**1b**)

Table 2. Reaction scope.



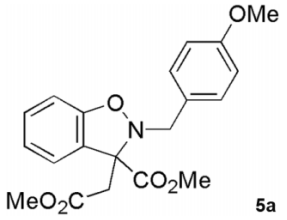
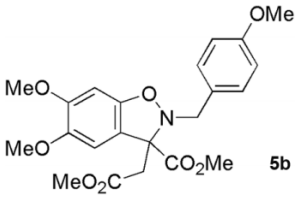
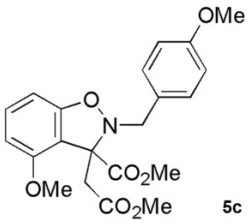
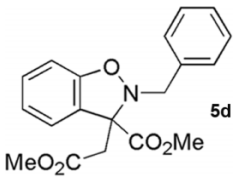
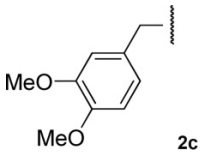
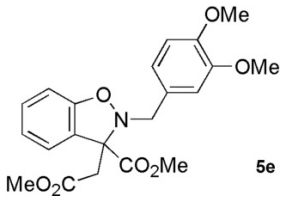
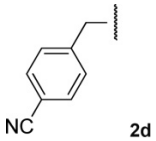
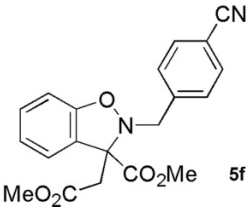
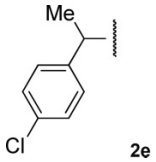
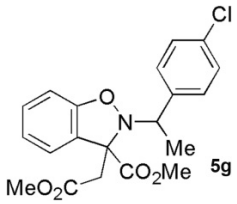
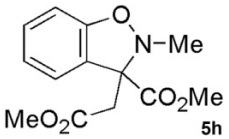
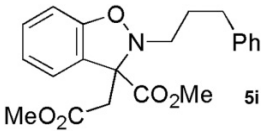
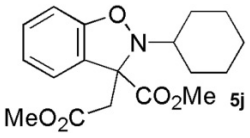
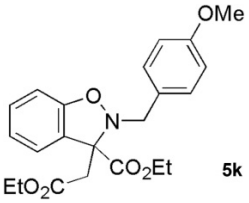
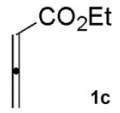
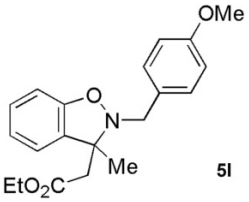
Entry	R^1 (**1**)	R^2 (**2**)	R^3 (**4**)	Product	Yield (%)[a]
1	Me (**1a**)	PMB (**2a**)	H (**4a**)	 **5a**	58[b]
2	Me (**1a**)	PMB (**2a**)	4,5-$(MeO)_2$ (**4b**)	 **5b**	46
3	Me (**1a**)	PMB (**2a**)	3-MeO (**4c**)	 **5c**	40[c]
4	Me (**1a**)	Bn (**2b**)	(**4a**)	 **5d**	46
5	Me (**1a**)	 **2c**	H (**4a**)	 **5e**	49
6	Me (**1a**)	 **2d**	H (**4a**)	 **5f**	Mixture

Table 2 (*concluded*).

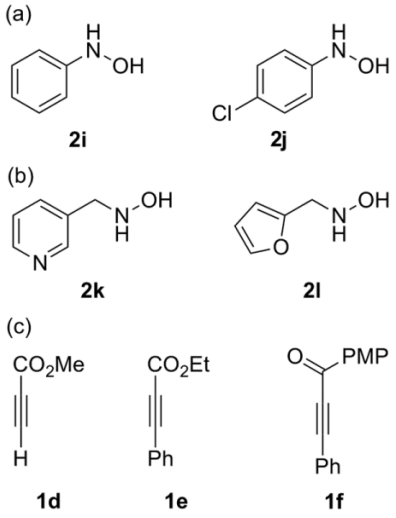
Entry	R^1 (**1**)	R^2 (**2**)	R^3 (**4**)	Product	Yield (%)[a]
7	Me (**1a**)	 **2e**	H (**4a**)	 **5g**	74 (1.8:1 dr)[d]
8	Me (**1a**)	Me (**2f**)	H (**4a**)	 **5h**	76[e]
9	Me (**1a**)	$Ph(CH_2)_3$ (**2g**)	H (**4a**)	 **5i**	64
10	Me (**1a**)	Cy (**2h**)	H (**4a**)	 **5j**	90
11	Et (**1b**)	PMB (**2a**)	H (**4a**)	 **5k**	75
12	 **1c**	PMB (**2a**)	H (**4a**)	 **5l**	36

Note: All reactions were carried out on a 0.4 mmol scale in 4 mL of MeCN for 3 h. PMB, *p*-methoxybenzyl; Cy, cyclohexyl; Bn, benzyl.
[a]Isolated yields.
[b]The use of microwave irradiation (100 W max, 80 °C, 30 min + 30 min) conditions afforded a 64% yield.
[c]The regiochemistry was analogously assigned by comparison with literature results (refs. 12a and 15a) and analysis of the ^{1}H NMR spectroscopy.
[d]The diastereomeric ratio (dr) was determined by crude ^{1}H NMR spectroscopy.
[e]The hydroxylamine was supplied as an HCl salt, and 1.2 equiv of Cs_2CO_3 was added to neutralize the acid.

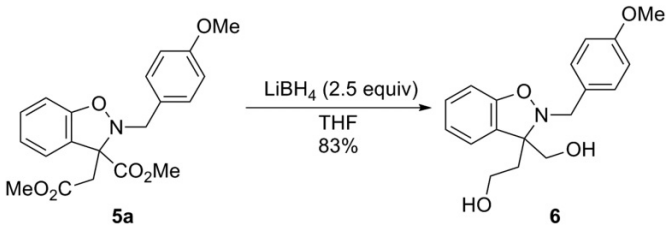
afforded a 75% yield of **5k** (Table 2, entry 11). An electron-poor allene (**1c**) could also smoothly afford **5l** in an unoptimized 36% yield (Table 2, entry 12). Thus, the one-pot three-component protocol could furnish dihydrobenzisoxazoles with three different handles for possible manipulation. Regretfully, the yields and the mass balance of some reactions remained less than satisfactory.

This protocol poses some limitations (Fig. 1). For example, *N*-arylhydroxylamines, such as **2i** and **2j**, react with DMAD reversibly[23,24] and thus *N*-aryldihydrobenzisoxazole derivatives are not accessible via this approach. Additionally, some hydroxylamines derived from heteroaromatic aldehydes, such as **2k** and **2l**, are unstable and not successfully employed either. It thus appears that the currently described protocol is more suitable for nonbenzylic aliphatic hydroxylamines (such as in Table 2, entries 8–10). Lastly, alkynes with only one electron-withdrawing group, such as **1d**, **1e**, and **1f**, are not sufficiently reactive to generate nitrones. To date, all attempts to employ

Fig. 1. Limitation of the protocol. (*a*) Hydroxylamines that form nitrones reversibly. (*b*) Unstable hydroxylamines. (*c*) Alkynes with insufficient reactivity.



Scheme 2. Reduction of the diester.



hydrazines in place of hydroxylamines to afford azomethine imine intermediates in situ have not been successful.

The stereochemistry in entry 7 (Table 2) was particularly worth mentioning. In Larock and co-workers' report,[15a] a cyclic nitrone with an embedded chiral center provided good diastereoselectivity. Since previous reports have indicated that nitrones employed in our chemistry are stereochemically defined (C=N bond adopting *E* geometry),[25] we were curious about the level of diastereoselectivity of the reaction involving nitrone **5g** in an open-chain A1,3 strain context. The experiment revealed a very modest level of stereoseletivity of 1.8:1, indicating that acyclic stereocontrol[26] in nitrone–aryne cycloaddition is difficult. A similar cycloaddition with alkenes in the literature provided an agreeable modest level of diastereoselectivity.[25]

As a useful extension of this protocol, the two ester groups can be further manipulated. For example, the simple reduction of **5a** using $LiBH_4$ afforded the corresponding diol **6** in an 83% yield (Scheme 2). Unfortunately, reduction with SmI_2 only afforded a complex mixture.

In summary, we have developed a one-pot protocol for the efficient synthesis of functionalized dihydrobenzisoxazoles from hydroxylamines, acetylenedicarboxylates, and arynes via in situ generation of nitrones. The protocol not only circumvents the necessity to isolate nitrones and thus is pot efficient, but also works with a different scope of nitrones. The stability of the hydroxylamines and nitrones poses the biggest limitation to the current method.[27]

Experimental section

All reagents purchased from commercial sources were used as received. THF and MeCN were distilled from Na/benzophenone and CaH_2, respectively. The silica gel for column chromatography was supplied as 300–400 mesh from Haiyang Chemicals (Qingdao, China).[28] Powdered CsF was used as received and stored in a dessicator.

All melting points are uncorrected. The ^1H and ^{13}C NMR spectra were referenced to the residual solvent signals (7.26 ppm for ^1H and 77.0 ppm for ^{13}C in $CDCl_3$).

General procedure

To an oven-dried 10 mL round-bottom flask equipped with a stirrer was added 0.48 mmol of the aryne precursor (1.2 equiv), followed by 0.4 mmol of the hydroxylamine. Dry MeCN (2 mL) was added and the mixture was stirred until it became homogeneous. A solution of dialkyl acetylenedicarboxylate (0.4 mmol) in MeCN (2 mL) was added dropwise, followed by 0.8 mmol of solid CsF (2 equiv) in one portion. The reaction mixture was stirred at 50 °C and monitored by TLC. Upon completion, the reaction mixture was poured into brine and extracted three times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether / EtOAc) to afford the dihydrobenzisoxazoles.

Compound 5a

Slightly yellow solid; mp 126–127 °C. R_f = 0.43 (petroleum ether / EtOAc, 4:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39 (dd, J = 7.6, 1.0 Hz, 1H), 7.36–7.31 (m, 2H), 7.25–7.19 (m, 1H), 6.96 (td, J = 7.5, 0.9 Hz, 1H), 6.92–6.87 (m, 2H), 6.77 (d, J = 8.1 Hz, 1H), 4.18 and 4.10 (ABq, J = 13.8 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 3.38 and 3.14 (ABq, J = 16.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 169.3. 159.0, 156.1, 130.0, 129.6, 128.9, 127.3, 125.0, 121.5, 113.7, 108.2, 74.3, 56.8, 55.2, 52.8, 51.8, 41.2. HR-MS electrospray ionization (ESI)) calcd for $C_{20}H_{22}NO_6$ (M + H): 372.1442; found: 372.1440.

Compound 5b

Slightly yellow oil. R_f = 0.23 (petroleum ether / EtOAc, 2:1). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.7 Hz, 2H), 6.95 (s, 1H), 6.89 (d, J = 8.7 Hz, 2H), 6.39 (s, 1H), 4.13 and 4.04 (ABq, J = 13.7 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 3.36 and 3.10 (ABq, J = 16.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 169.5, 159.0, 150.6, 150.6, 144.1, 130.0, 128.9, 117.0, 113.7, 108.4, 93.1, 74.9, 56.8, 56.7, 56.0, 55.2, 52.8, 51.8, 41.4. HR-MS (ESI) calcd for $C_{22}H_{26}NO_8$ (M + H): 432.1653; found: 432.1653.

Compound 5c

Colorless oil. R_f = 0.49 (petroleum ether / EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37 (m, 2H), 7.15 (t, J = 8.2 Hz, 1H), 6.92–6.83 (m, 2H), 6.43 (d, J = 8.1 Hz, 1H), 6.36 (dd, J = 8.1, 0.5 Hz, 1H), 4.30 and 4.20 (ABq, J = 13.8 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H), 3.45 and 3.28 (ABq, J = 15.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 169.3, 159.0, 157.3, 155.6, 130.9, 130.0, 129.3, 114.2, 113.7, 103.4, 100.8, 74.2, 57.5, 55.6, 55.2, 52.6, 51.6, 39.0. HR-MS (ESI) calcd for $C_{21}H_{24}NO_7$ (M + H): 402.1547; found: 402.1545.

Compound 5d

Colorless oil. R_f = 0.52 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.31 (m, 6H), 7.26–7.21 (m, 1H), 6.97 (td, J = 7.5, 0.9 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.28 and 4.20 (ABq, J = 14.0 Hz, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 3.41 and 3.18 (ABq, J = 16.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 169.3, 156.1, 136.9, 129.6, 128.7, 128.3, 127.5, 127.3, 124.9, 121.5, 108.2, 74.4, 57.3, 52.9, 51.9, 41.2. HR-MS (ESI) calcd for $C_{19}H_{20}NO_5$ (M + H): 342.1336; found: 342.1332.

Compound 5e

Colorless oil. R_f = 0.30 (petroleum ether / EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J = 7.1 Hz, 1H), 7.22 (td, J = 7.80, 1.0 Hz, 1H), 6.98–6.92 (m, 3H), 6.85 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 4.22 and 4.06 (ABq, J = 13.8 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.38 and 3.14 (ABq, J = 16.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 169.3, 156.1, 148.8, 148.4, 129.6, 129.3, 127.3, 125.0, 121.5, 121.0, 111.8, 110.9, 108.2, 74.4, 57.1, 55.84, 55.78, 52.9, 51.9, 41.2. HR-MS (ESI) calcd for $C_{21}H_{24}NO_7$ (M + H): 402.1547; found: 402.1549.

Compound 5g

Slightly yellow oil. R_f = 0.59 (petroleum ether / EtOAc, 4:1). This compound was obtained as a mixture of diastereomers. A very small quantity of the major isomer could be purified and characterized as such: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.22 (m, 6H), 6.96 (td, J = 7.6, 0.9 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 4.40 (q, J = 6.6 Hz, 1H), 3.57 (s, 3H), 3.48 (s, 3H), 3.27 and 2.81 (ABq, J = 16.7 Hz, 2H), 1.43 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 168.8, 156.4, 140.9, 133.2, 129.5, 129.2, 128.4, 128.3, 125.5, 121.5, 107.7, 74.7, 61.6, 52.6, 51.6, 42.4, 22.0. HR-MS (ESI) calcd for $C_{20}H_{21}ClNO_5$ (M + H): 390.1103; found: 390.1100. The minor isomer could not be purified.

Compound 5h

The reaction was performed in the presence of 1.2 equiv of Cs_2CO_3. The product was as slightly yellow oil. R_f = 0.41 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (dd, J = 7.6, 0.9 Hz, 1H), 7.25–7.19 (m, 1H), 6.97–6.91 (m, 1H), 6.80 (d, J = 8.1 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.24 and 3.09 (ABq, J = 16.8 Hz, 2H), 2.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 169.4, 156.1, 129.8, 126.8, 125.2, 121.7, 108.2, 74.7, 52.9, 52.0, 40.6, 40.2. HR-MS (ESI) calcd for $C_{13}H_{16}NO_5$ (M + H): 266.1023; found: 266.1019.

Compound 5i

Slightly yellow oil. R_f = 0.40 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (dd, J = 7.6, 0.8 Hz, 1H), 7.30–7.25 (m, 2H), 7.21–7.16 (m, 4H), 6.94 (td, J = 7.6, 0.8 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.26 and 3.04 (ABq, J = 16.7 Hz, 2H), 3.07–3.01 (m, 1H), 2.93–2.86 (m, 1H), 2.74 (t, J = 7.7 Hz, 2H), 2.11–2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 169.3, 156.0, 141.7, 129.6, 128.4, 128.3, 127.4, 125.8, 125.1, 121.5, 108.0, 74.5, 52.8, 52.4, 51.8, 40.5, 32.9, 29.4. HR-MS (ESI) calcd for $C_{21}H_{24}NO_5$ (M + H): 370.1649; found: 370.1646.

Compound 5j

Slightly yellow oil. R_f = 0.54 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (dd, J = 7.6, 0.8 Hz, 1H), 7.23–7.17 (m, 1H), 6.90 (td, J = 7.5, 0.9 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 3.36 and 3.03 (ABq, J = 16.2 Hz, 2H), 3.07 (tt, J = 10.7, 3.2 Hz, 1H), 1.91–1.48 (m, 6H), 1.36–1.06 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 170.1, 156.7, 129.4, 128.2, 124.3, 121.0, 107.1, 73.7, 62.9, 52.9, 51.7, 41.6, 31.3, 29.8, 25.6, 25.4, 25.1. HR-MS (ESI) calcd for $C_{18}H_{24}NO_5$ (M + H): 334.1649; found: 334.1649.

Compound 5k

Slightly yellow oil. R_f = 0.49 (petroleum ether/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dd, J = 7.6, 1.0 Hz, 1H), 7.37–7.33 (m, 2H), 7.22 (td, J = 8.0, 1.3 Hz, 1H), 6.98–6.93 (m, 1H), 6.92–6.89 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 4.37–4.09 (m, 6H), 3.81 (s, 3H), 3.38 and 3.12 (ABq, J = 16.5 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.8, 168.7, 159.0, 156.1, 130.0, 129.5, 129.1, 127.5, 125.0, 121.3, 113.7, 108.1, 74.3, 61.9, 60.8, 56.7, 55.2, 41.4, 14.0 (overlapped signal). HR-MS (ESI) calcd for $C_{22}H_{26}NO_6$ (M + H): 400.1755; found: 400.1750.

Compound 5l

Colorless oil. R_f = 0.39 (petroleum ether/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.33 (m, 2H), 7.21–7.15 (m, 2H), 6.97–6.89 (m, 3H), 6.79–6.76 (m, 1H), 4.14–4.05 (m, 2H), 4.06 and 3.90 (ABq, J = 13.6 Hz, 2H), 3.81 (s, 3H), 2.80 (s, 2H), 1.73 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 158.9, 155.6, 132.5, 130.0, 129.6, 128.6, 122.9, 121.2, 113.8, 108.5, 68.3, 60.4, 55.3, 55.2, 44.4, 20.6, 14.1. HR-MS (ESI) calcd for $C_{20}H_{24}NO_4$ (M + H): 342.1700; found: 342.1699.

Compound 6

To an oven-dried 10 mL round-bottom flask equipped with a stirrer was added **5a** (93 mg, 0.25 mmol). Dry THF (3 mL) was added and the solution was cooled to 0 °C. A $LiBH_4$ solution (2 mol/L in THF, 0.35 mL, 0.7 mmol, 2.5 equiv) was added dropwise. The reaction mixture was stirred at rt overnight. Glycerol (1 mL) was added and the mixture was stirred for 2 h before being poured into brine. It was extracted three times with EtOAc, and the combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography to afford **6** as a slightly yellow oil. R_f = 0.25 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.32 (m, 2H), 7.23–7.17 (m, 1H), 7.08 (dd, J = 7.5, 0.8 Hz, 1H), 6.98–6.95 (m, 1H), 6.93–6.89 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 4.25 and 4.20 (ABq, J = 13.9 Hz, 2H), 3.91–3.69 (m, 4H), 3.80 (s, 3H), 2.26–2.03 (m, 2H), OH protons show a br at ~3.0. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.0, 156.1, 130.1, 129.2 (2C), 128.5, 122.9, 121.4, 113.9, 108.3, 73.9, 65.2, 58.9, 55.2, 54.9, 34.7. HR-MS (ESI) calcd for $C_{18}H_{22}NO_4$ (M + H): 316.1543; found: 316.1541.

Supplementary data

Supplementary data are available with the manuscript through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0199.

Acknowledgments

This project was financially supported by the National Natural Science Foundation of China (No. 21002021) and the

Chinese Ministry of Education (Key Project No. 210127, and the Scientific Research Foundation for the Returned Overseas Chinese Scholars). We thank Dr. Jiang Zhou, Professor Shrong-Shi Lin (both Peking University), Mr. Huaiqiu Wang, and Professor Zheng Duan (both Zhengzhou University) for their help in the spectroscopic analysis.

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(24) The *N*- or *O*-arylation product(s) were detected.

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(27) Needless to mention, most of the unstable hydroxylamines and nitrones are problems for aryne cycloaddition with isolated nitrones as well.

(28) The R_f values obtained using this silica gel are greater than those obtained using silica gels typically supplied in Western countries.

Glycosyl fluorides from *n*-pentenyl-related glycosyl donors — Application to glycosylation strategies

Bert Fraser-Reid, J. Cristobal Lopez, Paloma Bernal-Albert, Ana M. Gomez, Clara Uriel, and Juan Ventura

Abstract: *n*-Pentenyl glycosides (NPGs) and *n*-pentenyl orthoesters (NPOEs) have been transformed into glycosyl fluorides by a variety of methods. In the case of NPGs, Barluenga's reagent, bis(pyridinium)iodonium(I)tetrafluoroborate (IPy_2BF_4), gives good yields of glycosyl fluorides when HF–pyridine complex is used as an additional fluoride source. NPOEs can be activated either by a combination of electrophilic iodonium (Barluenga's reagent) and HBF_4 or by the action of HF–pyridine complex. The ensuing glycosyl fluorides form a semiorthogonal pair of glycosyl donors when confronted with NPGs.

Key words: pentenyl glycosides, glycosyl fluorides, pentenyl orthoesters, glycosylation, orthogonal.

Résumé : Les glycosides de *n*-penténylе (GNP) et les orthoesters de *n*-penténylе (OENP) peuvent être transformés en fluorures de glycosyles par diverses méthodes. Dans les cas des GNP, le réactif de Barluenga, le tétrafluoroborate de bis(pyridinium)iodonium(I) (IPy_2BF_4) permet d'obtenir de bons rendements de fluorures de glycosyles si on utilise le complexe de HF–pyridine comme source additionnelle de l'ion fluorure. Les OENP peuvent être activés soit par une combinaison d'iodonium électrophile (tel le réactif de Barluenga) et de l'acide HBF_4 ou par l'action du complexe HF–pyridine. Les fluorures de glycosyles qui en résultent conduisent à la formation d'une paire semi-orthogonale de donneurs glycosyles lorsqu'ils sont confrontés à des glycosides de penténylе, GNP.

Mots-clés : glycosides de penténylе, fluorures de glycosyle, orthoesters de penténylе, glycosylation, orthogonal.

[Traduit par la Rédaction]

Introduction

Biologically active oligosaccharides are rarely simple uniform linear structures such as those found in other biopolymers.[1] Branched motifs are frequently encountered, and these substructures convey biological information and therefore cannot be ignored in view of their biological significance. These complex oligosaccharides present multiple challenges to laboratory synthesis because issues of regioselectivity, chemoselectivity, and stereoselectivity must be addressed.[2] Frush and Isbell's[3] discovery of neighboring group participation 71 years ago showed how the last of these three selectivities, 1,2-trans stereoselectivity, could be optimized in donor–acceptor coupling.

Regio- and chemo-selectivities are principles of interest to our groups in view of their potential for reducing the time-consuming, and frequently frustrating, demands of protect–deprotect synthetic strategies. Regioselectivity requires that a donor be induced to display a preference for one of several available hydroxyls of an acceptor, thereby reducing the need to protect all hydroxyls except the targeted one. Chemoselectivity is required when two (or more?) donors are prone to the same activation process, but one must be preferably triggered. The 20-year-old armed–disarmed strategy is a case in point.[4]

Prior to these developments, the concept of orthogonal glycosylation had been introduced by Ogawa and co-workers[5] in 1994. The strategy involves the coupling of two *potential* donors with *different* leaving groups, one of which can be activated without disturbing the other, which can then become an acceptor. Glycosyl fluorides were one of the donors featured in the original experiments and, since their emergence in 1981,[6] have proven to be valuable in glycosylation strategies.[7] The interest in these glycosyl donors, because of their enhanced stability compared with other glycosyl halides, has continued to flourish over the last two decades,[8] and a variety of methods are now available for their activation.[9]

Results and discussion

Glycosyl fluorides from *n*-pentenyl glycosides

In view of these properties, the preparation of glycosyl fluorides continues to be a topic of interest. *n*-Pentenyl glycosyl donors are ready precursors of other donors, e.g., glycosyl bromides[10] and trichloroacetimidates,[11] hence, we were interested in adding glycosyl fluorides to this list. *n*-Pentenyl donors are usually triggered by halonium ions[4d] and (or) acids.[12] In view of the latter, the Barluenga reagent, bis(pyridinium) iodonium(I)tetrafluoroborate (IPy_2BF_4), was of interest as a possible electrophilic agent.[13,14] In this connection, it should

Received 24 July 2012. Accepted 28 August 2012. Published at www.nrcresearchpress.com/cjc on 2 January 2013.

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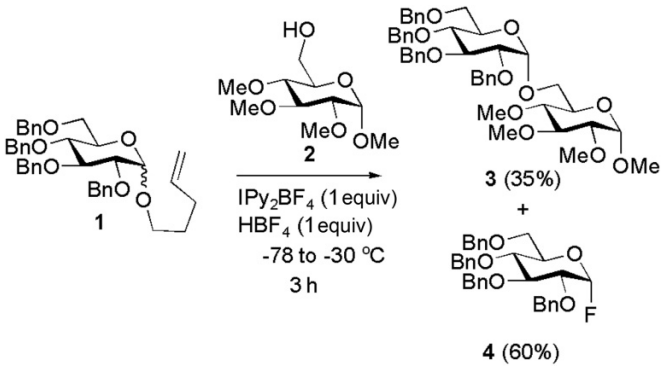
Scheme 1. Attempted activation–glycosylation of **2** with NPG **1**.



be noted that Clausen and Madsen[15] previously converted *n*-pentenyl glycosides (NPGs) to glycosyl fluorides.

This interest was sparked by attempts to glycosylate acceptor **2** with donor **1** using the Barluenga reagent, along with an equimolar amount of HBF_4 to neutralize nucleophilic pyridine that is released during the reaction. As shown in Scheme 1, the hoped-for disaccharide (**3**) was obtained in a 35% yield; however, the formation of twice as much glycosyl fluoride (**4**) indicated that fluoride ion was competing strongly for the donor (**1**).

The 2:1 formation of products **4** and **3** indicated the potential of the process as a route to glycosyl fluorides.[16] The chances of improving glycosyl fluoride formation should be enhanced by removing the acceptor **2** and increasing fluoride ion supply.

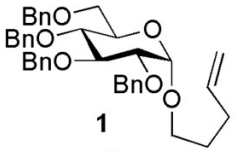
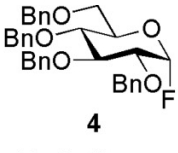
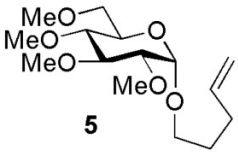
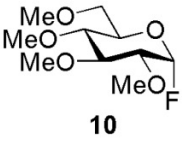
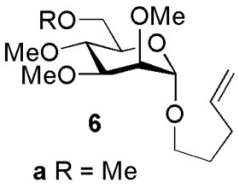
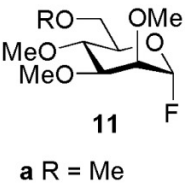
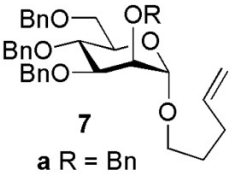
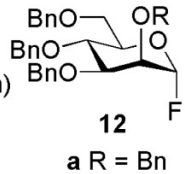
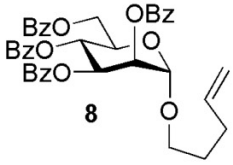
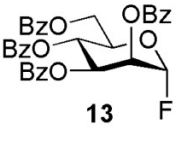
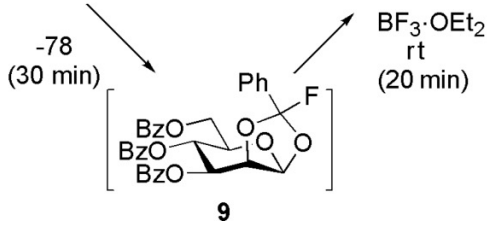
Accordingly, a collection of NPGs, Table 1 (**1**, **5**–**8**), armed and disarmed, with diverse protecting groups, was treated at −40 °C with 1 equiv of IPy_2BF_4 and a slight excess of HBF_4. Entries *i*–*v* of Table 1 showed that the formation of fluorides **4** and **10**–**13**, respectively, was usually complete in 10–40 min (TLC), with very good to excellent results. Notably, silyl protecting groups were compatible with the reaction conditions, as is clear from the conversion of NPG **6b** to glycosyl fluoride **11b** (Table 1, entry *iii*).

The reaction of the NPG tetrabenzoate **8** (Table 1, entry *v*) requires special comment. Under the indicated conditions of Table 1, but with a temperature of –78 °C, the starting material (**8**) disappeared after 30 min to give a stable substance. Exposing the latter to $BF_3{\cdot}OEt_2$ for 20 min led to the tetrabenzoyl glycosyl fluoride **13**. The intermediacy of the orthoacyl fluoride **9** was indicated, with this possibility being supported by the prior work of Griffith and Hindsgaul.[17]

Our interest in the use of partially protected NPG donors for regioselective glycosylations prompted us to examine the synthesis of comparable glycosyl fluoride donors (Table 2). Accordingly, the partially protected NPG mannoside **14** was treated with 2 equiv of an IPy_2BF_4/HBF_4 mixture at –55 °C for 10 min. As seen from entry *i* (Table 2), the desired fluoride (**16**) was obtained in a 42% yield, but was accompanied by 15% of disaccharide **17**. The gluco analog **15** gave an equal distribution of products, **18** and **19** (40% and 15%, respectively). Obviously the concentration of nucleophilic fluoride was not enough to preclude self-coupled formation of the disaccharides.

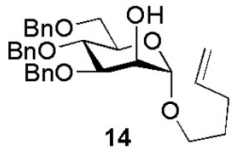
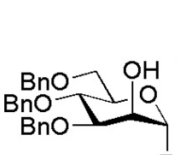
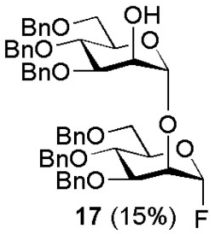
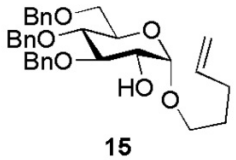
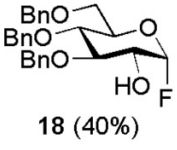
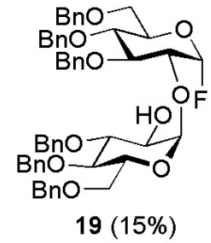
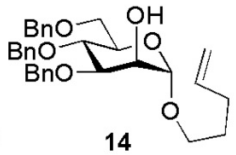
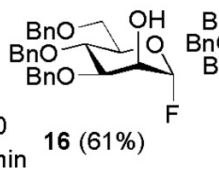
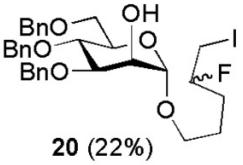
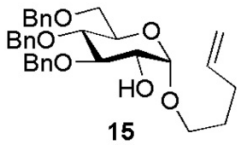
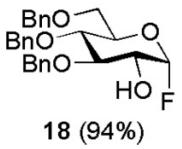
The HF–pyridine complex (or Olah's reagent) has been used as a source of nucleophilic fluoride,[18,19] so it was a

Table 1. IPy_2BF_4/HBF_4 mediated transformation of *n*-pentenyl glycosides to glycosyl fluorides in CH_2Cl_2.

Entry	Substrate	Temp. (°C) (time)	Product	Yield (%)
i	 **1**	-40 (30 min)	 **4**	83
ii	 **5**	-40 (15 min)	 **10**	99
iii	 **6** **a** R = Me **b** R = TBDPS	-40 (15 min)	 **11** **a** R = Me **b** R = TBDPS	94 75
iv	 **7** **a** R = Bn **b** R = Bz	-40 (15-30 min)	 **12** **a** R = Bn **b** R = Bz	94 90
v	 **8**	-78 (30 min)	 **13**	75
		 **9**	$BF_3{\cdot}OEt_2$ rt (20 min)	

logical choice as a partner for the Barluenga reagent in our efforts to enhance the formation of glycosyl fluorides.[20] Accordingly, NPGs **14** and **15** were exposed to IPy_2BF_4 in the presence of an excess of Olah's reagent at low temperature. Indeed, the use of a 2:10 ratio of IPy_2BF_4/HF (Table 2, entry *iii*) on mannoside **14** gave a considerable increase in the yield of the desired fluoride, **16**. However, this was accompanied by a substantial amount of compound **20**, resulting from iodofluorination of the olefinic residue of the precursor. Lowering the ratio of the fluoride source by 50% to 2:5 (Table 2, entry *iv*) had the desired effect in that the yield of fluoride **16**

Table 2. IPy_2BF_4/HBF_4 and IPy_2BF_4/HF–pyridine mediated transformation of partially unprotected *n*-pentenyl glycosides to glycosyl fluorides.

Entry	Substrate	IPy_2BF_4(equiv)/HBF_4 or HF (equiv)	Temp., time	Product (Yield)
i	 **14**	2 / (HBF_4) 2	-55 °C, 10 min	 **16** (42%)  **17** (15%)
ii	 **15**	2 / (HBF_4) 2	-55 °C, 1 h	 **18** (40%)  **19** (15%)
iii	 **14**	2 / (HF) 10	-55 °C, 10 min	 **16** (61%)  **20** (22%)
iv	**14**	2 / (HF) 5	-55 °C, 10 min	**16** (85%) **20** (10%)
v	 **15**	2 / (HF) 10	-40 °C, 1h	 **18** (94%)

had increased to 85%. Unfortunately, the iodofluorination product **20** was still produced in a substantial amount.

With the gluco NPG **15** (Table 2, entry *v*), the desired fluoride **18** was obtained in a 94% yield with no evidence of the corresponding iodofluorination product. Notably, this result was obtained even though the ratio of reagents (IPy_2BF_4/HF, 2:10) was very favorable for iodofluorination (Table 2, entries *iii* and *iv*).

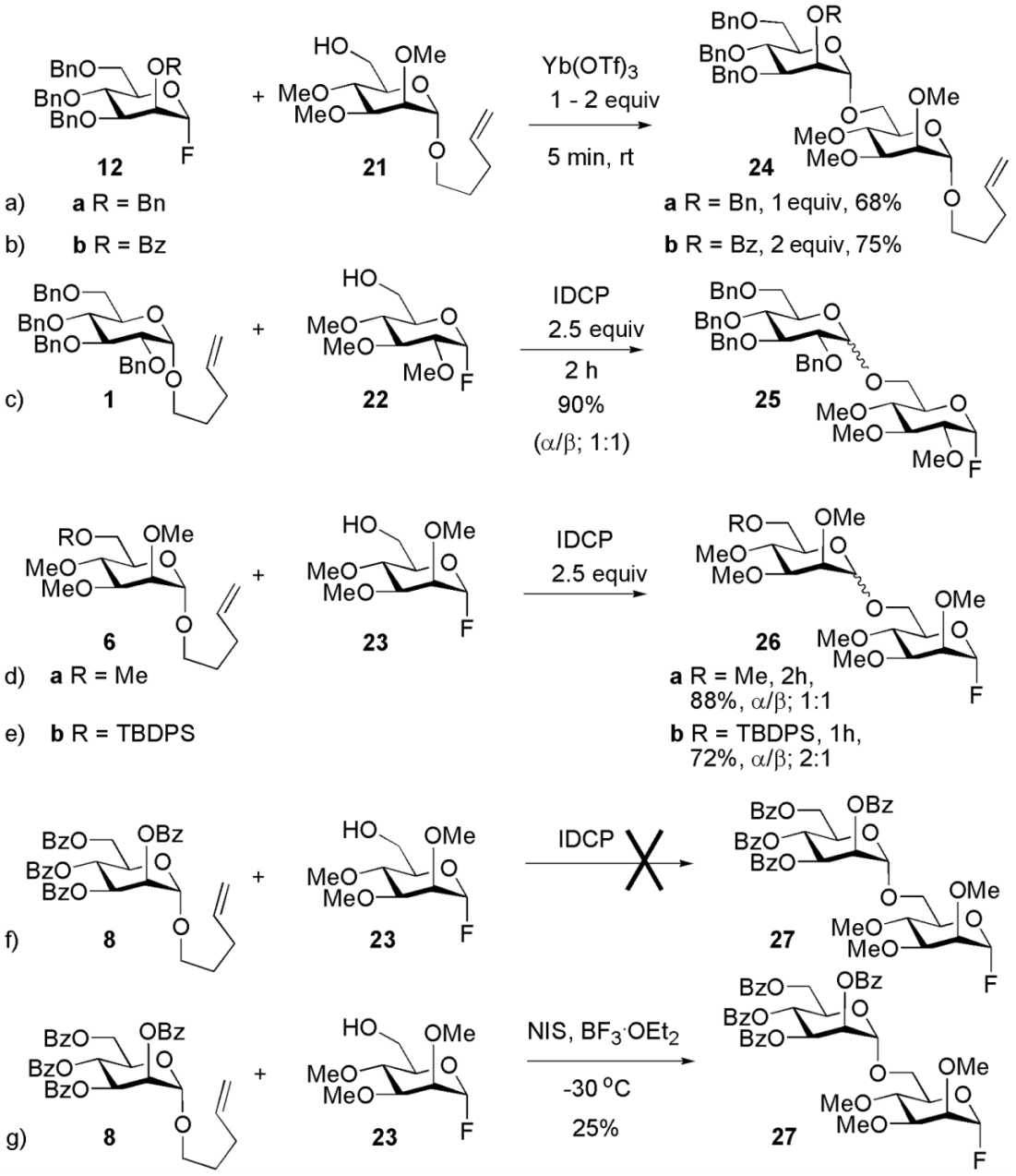
Glycosyl fluorides and *n*-pentenyl glycosides as semiorthogonal glycosyl donors

With the availability of glycosyl fluorides and NPGs, the possibility of orthogonal coupling between both was now explored (Scheme 2). To activate the glycosyl fluoride as a donor, ytterbium triflate ($Yb(OTf)_3$) was chosen as the fluorophilic agent. Schemes 2*a* and 2*b* record the results of coupling armed and disarmed donors **12a** and **12b**, respectively, with the NPG **21** as acceptor. Disaccharides **24a** and **24b** were obtained in encouraging yields of 68% and 75%, respectively.

Reversing the roles of orthogonal donor and acceptor required a source of iodonium ions for activating the NPG donor. Iodonium dicollidine perchlorate (IDCP),[21] which has served us well in the past,[22] was chosen for coupling glycosyl fluoride acceptors **22** and **23** with armed gluco (**1**, Scheme 2*c*) and manno (**6a** and **6b**, Scheme 2*d* and 2*e*, respectively) donors. Products **25**, **26a**, and **26b** were obtained in excellent yields of 90%, 88%, and 72%, respectively, albeit as α/β mixtures. The result in Scheme 2*e* is noteworthy because of the survival of the silyl protecting group under the reaction conditions.

The donors in Scheme 2*c*–2*e*, were armed; however, the disarmed counterpart, **8**, (Scheme 2*f*) failed to give **27** with IDCP as the electrophile. The use of *N*-iodosuccinimide (NIS) with $BF_3{\cdot}OEt_2$ proved better, although product **27** was obtained in only in a 25% yield. Because of these facts, the glycosyl fluoride – NPG couple could be best described as a semiorthogonal donors pair of donors.[23]

Scheme 2. *n*-Pentenyl glycosides (NPGs) and glycosyl fluorides as a pair of semiorthogonal donors.



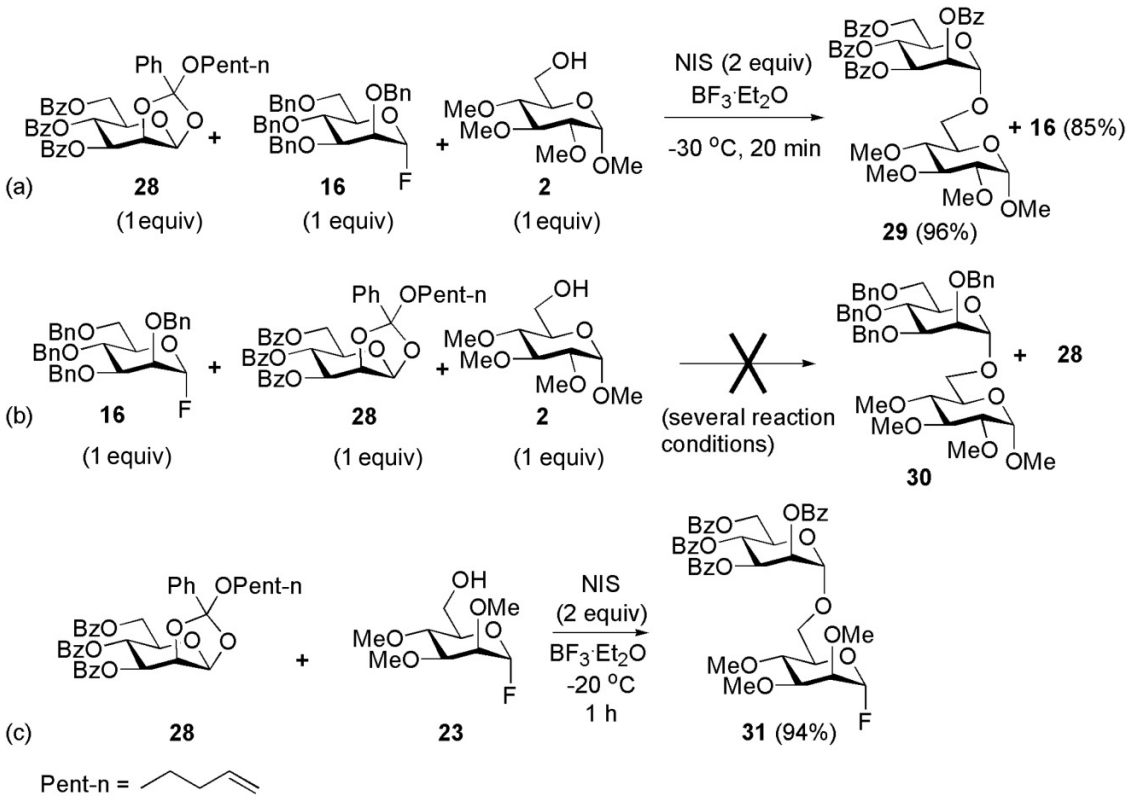
n-Pentenyl orthoesters (NPOEs) are ~15 kcal (1 cal = 4.184 J) more reactive than the corresponding NPG,[24] and on that basis, they should serve as better progenitors of glycosyl fluorides. This possibility was tested by presenting acceptor **2** (1 equiv) to equimolar amounts of NPOE **28** and the armed fluoride **16** along with NIS (2 equiv) and $BF_3{\cdot}OEt_2$. After 20 min at −30 °C, glycosylation had occurred by the NPOE only to give the tetrabenzoylated disaccharide **29** in a 96% yield (Scheme 3*a*), with the glycosyl fluoride being recovered to the extent of 85%.

This result suggested that the NPOE was the superior donor under the conditions used in Scheme 3*a*. Attempts were made to enforce glycosylation of acceptor **2** by armed glycosyl fluoride **16**, in the presence of NPOE **28**, by the use of various fluorophilic agents, but all failed to produce disaccharide **30** (Scheme 3*b*). These experiments confirmed that activation of a glycosyl fluoride in the presence of an NPOE is highly unlikely.

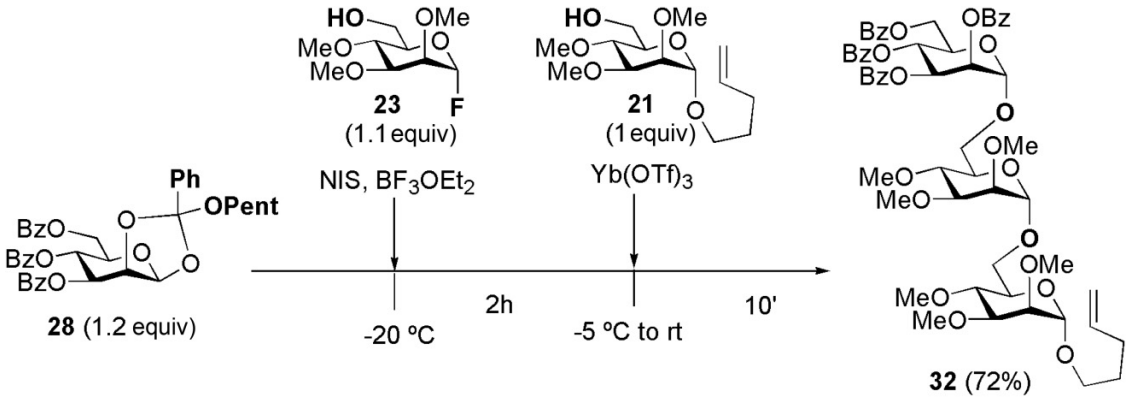
Accordingly, chemoselective coupling of NPOE **28** with the glycosyl fluoride acceptor **23** went smoothly (Scheme 3*c*) to give disaccharide **31** in a 94% yield.

In view of the foregoing results, a one-pot synthesis using three reactants (**21**, **23**, and **28**), each of which is a potential donor, and two of which (**21** and **23**) are potential acceptors, is shown in Scheme 4. Thus, glycosyl fluoride **23** served as acceptor to NPOE donor **28** under NIS/$BF_3{\cdot}OEt_2$ activation at −20 °C. After 2 h, NPG **21** was presented, as an acceptor, for glycosylation by the putative disaccharide under activation by $Yb(OTf)_3$ at room temperature. After 10 min, the

Scheme 3. Competition experiments for the chemoselective activation of *n*-Pentenyl orthoesters (NPOEs) in the presence of glycosyl fluorides.



Scheme 4. One-pot synthesis of trisaccharide **32**.



n-pentenyl trisaccharide **32** was obtained in a 72% yield as a single (α,α,α) isomer.

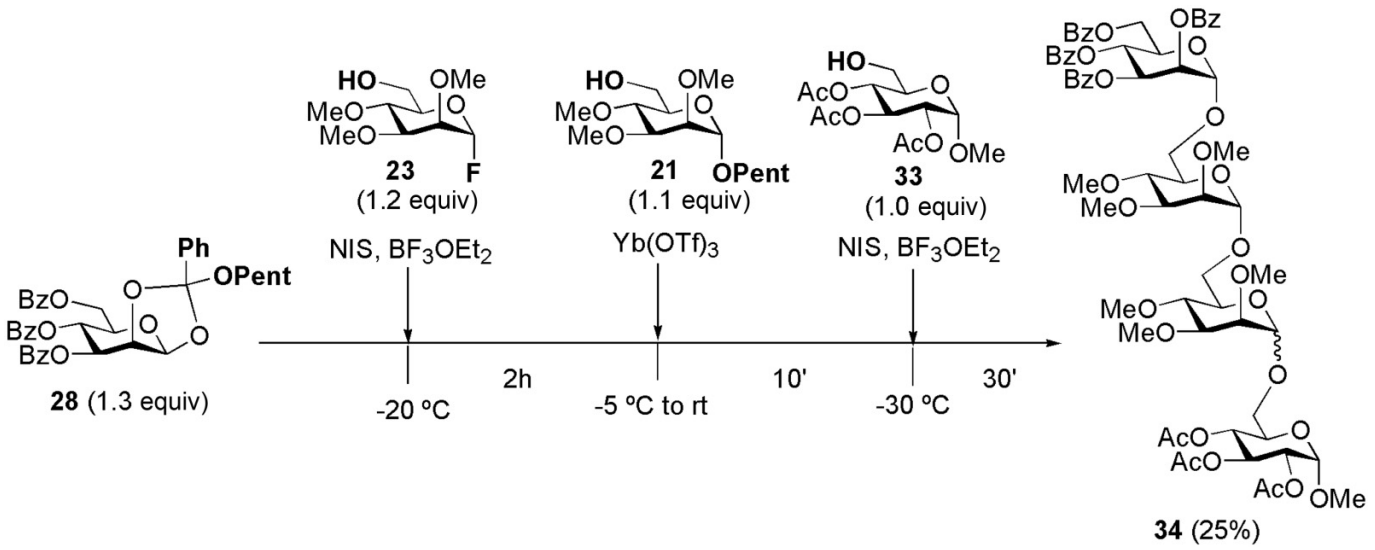
Along this line, and taking full advantage of the knowledge gained in this work, a further extension could be made to the one-pot synthesis in Scheme 4. Thus, in Scheme 5, methyl glucoside **33** was added (to **23** and **21**) as a third acceptor, which resulted in the one-pot synthesis of linear tetrasaccharide **34** (obtained as an α/β mixture). The low yield in this transformation was ascribed to the poor reactivity of acetylated acceptor **33** towards the intermediate *n*-pentenyl trisaccharide donor. In this sense, a considerable amount of hemiacetal arising from the trisaccharide was observed in the reaction mixture.

Glycosyl fluorides from furanosyl 1,2-orthoesters

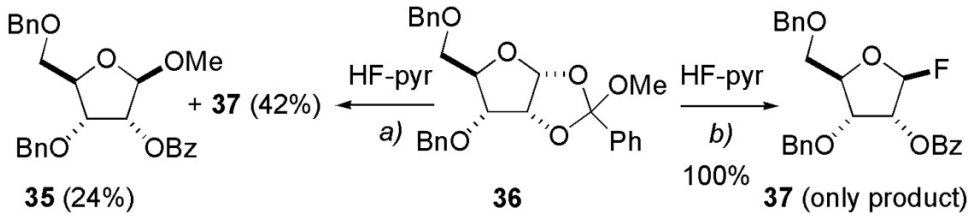
We were interested to see whether the previously discussed transformations of pyranosyl NPOEs could be extended to recently described furanosyl counterparts.[25,26]

Our exploratory work revealed the need for a different operational procedure than that used with the pyranose systems because the furanosyl substrates are much more acid-sensitive. It is crucial that a solution of the furanosyl orthoester in CH_2Cl_2 be added to the reaction mixture of HF–pyridine in CH_2Cl_2 rather than in the reverse order. Otherwise, with NPOE **36**, for example, rearrangement to the corresponding alkyl glycoside **35** was an important reaction course compared with that of the desired glycosyl fluoride **37** (Scheme 6).

Scheme 5. One-pot synthesis of tetrasaccharide **34**.



Scheme 6. Transformation of 1,2-orthoester **36** to furanosyl fluoride **37** by treatment with HF–pyridine complex. (*a*) Addition of HF–pyridine complex to a solution of **36** in CH_2Cl_2. (*b*) Addition of **36** to a precooled solution of HF–pyridine in CH_2Cl_2.



With this precaution implemented, the *ribo*-NPOE **38a** gave the fluoride **44** quantitatively in ~10 min (Table 3, entry *i*). The dibenzoyl and dibenzyl arabino substrates, **39a** and **40a**, respectively, behaved similarly, affording fluorides **45** and **46** in 95% and 91% yields, respectively (Table 3, entries *ii* and *iii*). These results suggested that the nature of the protecting groups at O3 and O5 did not have a major effect on the formation of the glycosyl fluorides.

The partially protected analogs with a free C3–OH gave distinctly different results. The arabino-NPOE **41** was converted to the fluoride **47** in a 91% yield (Table 3, entry *vii*). In contrast, the ribo counterpart **42** gave only a 53% yield of fluoride **48** (Table 3, entry *viii*).

Not surprisingly, a free C5–OH was unacceptable. Thus, diol **43** furnished the 1,5-anhydro derivative **49** upon treatment with HF–pyridine (Table 3, entry *ix*).

The use of these furanosyl fluorides with other donors for orthogonal coupling leading to oligofuranosides was tested as shown in Scheme 7. Glycosyl fluoride **47**, when presented to NPOE **38a** under activation with NIS/Yb(OTf)$_3$, gave a product that was presumed to be disaccharide **50**. This was directly treated with NPG **51** under activation of $BF_3{\cdot}OEt_2$, which led to trisaccharide **52**.

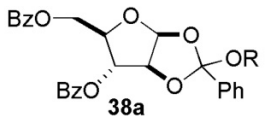
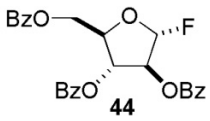
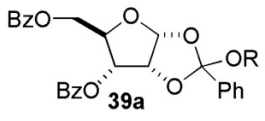
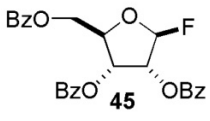
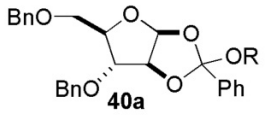
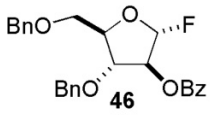
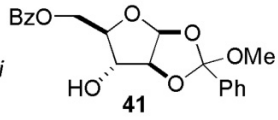
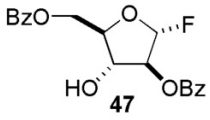
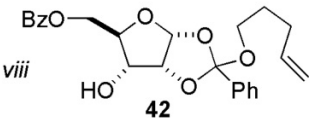
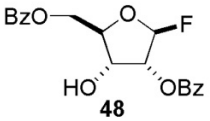
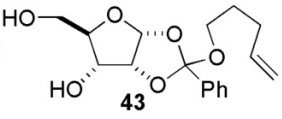
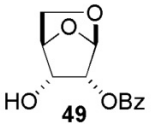
Conclusion

NPGs and NPOEs can be transformed into glycosyl fluorides by a variety of methods, which involve the use of electrophilic iodonium and nucleophilic fluoride. In the case of NPGs, Barluenga's reagent gives good yields of glycosyl fluorides when HF–pyridine complex is used as an additional fluoride source. NPOEs can be activated by a combination of electrophilic iodonium (Barluenga's reagent) and HBF_4 or by action of HF–pyridine complex in which acidic triggering of the pentenyl moiety is accompanied by the fluoride nucleophile present in Olah's reagent. Furthermore, the ensuing glycosyl fluorides form a semiorthogonal pair of glycosyl donors when confronted with NPGs.

Experimental section

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained for solutions in $CDCl_3$ using either a 300, 400, or a 500 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were assigned with the assistance of two-dimensional (2D) correlation spectroscopy (COSY) and 2D heteronuclear single quantum correlation (HSQC) experiments. Optical rotations were determined for solutions in chloroform at 25 °C. Column chromatography was performed on silica gel (230−400 mesh). TLC was conducted in precoated Kiesel gel 60 F_{254} (Merck). Detection was first by UV light (254 nm), then charring with a 1:20:4 solution of sulfuric acid / acetic acid / H_2O. All solvents were purified by distillation over drying agents or by elution through a PURE SOLV purification system. A time-of-flight (TOF) mass analyzer was used for the HR-MS. Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium

Table 3. Reaction of 1,2-orthoesters **38**−**43** with HF–pyridine complex in CH_2Cl_2.

Entry	Substrate	HF–pyridine (equiv)	Product	Yield (%)
i	 **38a**	20	 **44**	95
ii	**38b**	20	**44**	79
iii	 **39a**	20	 **45**	100
iv	**39b**	20	**45**	100
v	 **40a**	40	 **46**	91
vi	**40b**	40	**46**	93
vii	 **41**	20	 **47**	91
viii	 **42**	20	 **48**	53
ix	 **43**	20	 **49**	40

Note: R = *n*-pentenyl for series **a**; R = Me for series **b**.

sulfate was used for drying solutions. (NPGs) **1**, **5**–**8**, **14**–**15**, and **21**, pyranose orthoester **28**, and furanose orthoesters **36** and **38**–**43** were prepared following previously described procedures.[27] The exchange of substituents at the different hydroxyl groups was carried out following routine procedures.[28]

Attempted glycosylation of compound 2 with NPG 1, mediated by IPy_2BF_4

A solution of IPy_2BF_4 (74.4 mg, 0.24 mmol) in dry CH_2Cl_2 (2 mL) under argon and cooled to −78 °C was treated with tetrafluoroboric acid (27 μL, 0.24 mmol). After 5 min, a solution of the NPG **1** (122 mg, 0.23 mmol) and the glycosyl acceptor **2** (23.6 mg, 0.11 mmol) dissolved in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred at −78 °C for 30 min after which time it was allowed to warm to −30 °C and then stirred for an additional 2 h. The reaction mixture was then diluted with dichloromethane (30 mL) and washed with 10% aqueous sodium thiosulphate containing sodium bicarbonate and water. The organic layer was dried and concentrated and the ensuing residue was purified by flash chromatography (hexane/EtOAc, 8:2 to 1:1) to provide fluoride **4**[29] (72 mg, 60%) and disaccharide **3** (27 mg, 35%).

*Methyl 2,3,4-tri-*O*-methyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3)*

^{1}H NMR (300 MHz) δ: 7.34−7.15 (m, 20H), 5.02 (d, J = 11.1 Hz, 1H), 4.91 (d, J = 10.8 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 9.9 Hz, 1H), 4.75 (d, J = 11.3 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 10.9 Hz, 1H), 4.48 (m, 1H), 4.20 (m, 1H), 3.78–3.37 (m, 12H), 3.62 (s, 3H), 3.50 (s, 3H), 3.47 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (75 MHz) δ: 138.5, 138.4, 138.2, 138.1, 128.4 (×2), 128.3 (×6), 128.0 (×2), 127.9 (×2), 127.8 (×2), 127.7 (×2), 127.6 (×2), 127.5 (×2), 103.9, 97.3, 84.8, 83.4, 82.1, 81.7, 79.8, 77.9, 75.7, 75.0 (×2), 74.9, 73.4, 69.8, 69.0, 68.8, 60.8, 60.4, 58.9, 55.1. Anal. calcd for $C_{44}H_{54}O_{11}$ (758.37): C 69.64, H 7.17; found: C 69.30, H 7.35.

*2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (4)*

$[\alpha]_D$ +10.7 (*c* 0.53, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.15–7.31 (m, 20H), 5.56 (dd, J = 53.2, 2.6 Hz, 1H), 4.98–4.45 (m, 8H), 3.99 (t, J = 9.6 Hz, 1H), 3.94 (m, 1H) 3.79 (m, 1H), 3.65 (m, 1H), 3.57 (ddd, J = 25.7, 9.6, 2.6 Hz, 1H). Atmospheric pressure ionization and electrospray ionization (API–ES) positive: 565.2 $(M + Na)^+$. Anal. calcd for $C_{34}H_{35}O_5F$ (542.65): C 75.26, H 6.50; found: C 75.3, H 6.64.

General procedure A — IPy_2BF_4-mediated transformation of NPGs to glycosyl fluorides

A solution of IPy_2BF_4 (44.6 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) under argon and cooled to −40 °C was treated with tetrafluoroboric acid (13 μL, 0.12 mmol). After 5 min, a solution of the NPG or orthoester (0.10 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added. When all the starting material disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated sodium bicarbonate, and water. The organic layer was then dried and concentrated and the residue was purified by flash chromatography.

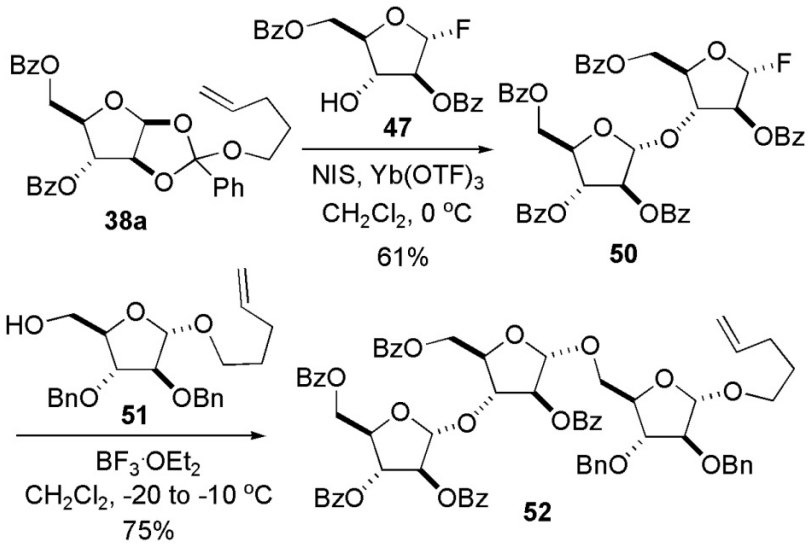
General procedure B — Reaction of partially unprotected NPGs with IPy_2BF_4/HBF_4

A solution of IPy_2BF_4 (44.6 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) under argon and cooled to −40 °C was treated with tetrafluoroboric acid (13 μL, 0.12 mmol). After 5 min, a solution of the NPG (0.10 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added. When all the starting material disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated sodium bicarbonate, and water. The organic layer was then dried and concentrated and the residue was purified by flash chromatography.

General procedure C — IPy_2BF_4/HF–pyridine-mediated transformation of partially unprotected NPGs to glycosyl fluorides

A solution of IPy_2BF_4 (74.2 mg, 0.2 mmol) in dry CH_2Cl_2 (3 mL) was cooled to −40 °C. HF–pyridine complex (5, 10, or 20 mmol) was then added and the resultant solution was stirred for 5 min. A solution of the NPG (0.1 mmol) in dry CH_2Cl_2 (2 mL) was then added dropwise. The resultant solution was

Scheme 7. Stepwise synthesis of trisaccharide **52**.



stirred for 20 min at −40 °C. The reaction was then diluted with methylene chloride (20 mL) and the resultant solution was carefully added to an aqueous solution containing $NaHCO_3$ and $Na_2S_2O_3$. The resulting layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc) afforded the corresponding glycosyl fluorides.

General procedure D — HF–pyridine mediated transformation of 1,2-orthoesters to glycosyl fluorides

A solution of the 1,2-orthoester (1 equiv) in dry CH_2Cl_2 (5 mL/mmol) was added to a solution of HF–pyridine (20 equiv unless otherwise specified) in dry CH_2Cl_2 (1 mL/mmol) under argon and cooled to −40 °C. After 5−10 min, when all the starting material had disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched by saturated aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography eluting with a mixture of hexane and ethyl acetate to afford the pure products.

*2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl fluoride (10)*

This compound was prepared according to General procedure A from *n*-pentenyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (**5**; 60.8 mg, 0.2 mmol). Silica gel chromatography (hexane/EtOAc, 7:3) provided pure **10** (50 mg, quantitative yield). ^{1}H NMR (300 MHz) δ: 5.66 (dd, J = 53.3, 2.6 Hz, 1H), 3.80–3.75 (m, 1H), 3.64 (s, OMe, 3H), 3.62–3.38 (m, 3H), 3.54 (s, OMe, 3H), 3.53 (s, OMe, 3H), 3.40 (s, OMe, 3H), 3.28 (t, J = 9.4 Hz, 1H), 3.19 (ddd, J = 25.6, 9.4, 2.6 Hz, 1H). ^{13}C NMR (75 MHz) δ: 104.9 (d, J = 224.8 Hz), 82.7, 81.2 (d, J = 24.6 Hz), 78.2, 72.3 (J = 4.0 Hz), 70.2, 60.9, 60.5, 59.1 (×2). API-ES positive: 477.3 $(2M + H)^+$. Anal. calcd for $C_{10}H_{19}O_5F$ (238.12): C 50.41, H 8.04; found: C 50.30, H 8.28.

*2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranosyl fluoride (11a)*

This compound was prepared according to General procedure A from *n*-pentenyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside (**6a**; 60.8 mg, 0.2 mmol). Silica gel chromatography (hexane/EtOAc, 7:3) provided **11a** (45 mg, 94%). $[\alpha]_D$ +28.7 (c 1.5, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 5.65 (dd, J = 1.6, 50.2 Hz, 1H), 3.76−3.58 (m, 6H), 3.51 (s, OMe, 3H), 3.50 (s, OMe, 3H), 3.49 (s, OMe, 3H), 3.39 (s, OMe, 3H). ^{13}C NMR (75 MHz) δ: 105.5 (d, J = 220.8 Hz), 80.4 (d, J = 2.0 Hz), 75.8 (d, J = 34.6 Hz), 75.4, 73.6 (d, J = 2.5 Hz), 60.6, 59.5, 59.2, 58.0. API-ES positive: 477.3 $(2M + H)^+$, 261.1 $(M + Na)^+$. Anal. calcd for $C_{10}H_{19}O_5F$ (238.12): C 50.41, H 8.04; found: C 50.17, H 7.96.

*6-*O*-tert-Butyldiphenylsilyl-2,3,4-*O*-tri-*O*-methyl-α-D-mannopyranosyl fluoride (11b)*

This compound was prepared according to General procedure A from *n*-pentenyl 6-*O*-*tert*-butyldimethylsilyl-2,3,4-*O*-tri-*O*-methyl-α-D-mannopyranoside (**6b**; 53 mg, 0.1 mmol). Silica gel chromatography (hexane/EtOAc, 8:2) provided **11b** (39.3 mg, 85%). $[\alpha]_D$ +26.5 (c 1.2, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.75−7.69 (m, 5H), 7.43–7.35 (m, 5H), 5.72 (dd, J = 50.5, 1.9 Hz, 1H), 3.97 (dd, J = 11.5, 3.4 Hz, 1H), 3.85 (t, J = 9.5 Hz, 1H), 3.85 (dd, J = 11.5, 1.7 Hz, 1H), 3.74 (m, 1H), 3.67−3.63 (m, 1H), 3.57 (s, 3H), 3.56 (m, 1H), 3.55 (s, 3H), 3.54 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (75 MHz) δ: 135.9 (×2), 135.6 (×2), 133.8, 133.3, 129.5 (×2), 127.6 (×2), 127.5 (×2), 105.6 (d, J = 219.4 Hz), 80.4, 75.9, 75.0, 74.8, 62.3, 60.7, 58.9, 57.9, 26.7 (×3), 19.4. API-ES positive: 480.3 $(M + NH_4)^+$, 485.3 $(M + Na)^+$. Anal. calcd for $C_{25}H_{35}O_5FSi$ (462.22): C 64.9, H 7.63; found: C 65.02, H 7.58.

*2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl fluoride (12a)*

This compound was prepared according to General procedure A from *n*-pentenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (**7a**; 60.8 mg, 0.1 mmol). Silica gel chromatography (hexane/EtOAc, 9:1) provided pure **12a** (51 mg, 94%).[30] $[\alpha]_D$ +25.9 (c 0.56, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.35–7.18 (20H, m), 5.60 (d, J = 50.6 Hz, 1H), 4.88 (d, J =

10.8 Hz, 1H), 4.81 (d, J = 12.3 Hz, 1H), 4.70–4.63 (4H, m), 4.56–4.53 (2H, m), 4.08 (t, J = 9.7 Hz, 1H), 3.93–3.88 (3H, m), 3.79 (dd, J = 11.0, 4.5 Hz, 1H), 3.72 (d, J = 10.9 Hz, 1H). API-ES positive: 565.3 $(M + Na)^+$. Anal. calcd for $C_{34}H_{35}FO_5$: C 75.26, H 6.50; found: C 75.16, H 6.45.

2-O-Benzoyl-3,4,6-O-tri-O-benzyl-α-D-mannopyranosyl fluoride (12b)

This compound was prepared according to General procedure A from *n*-pentenyl 2-*O*-benzoyl-3,4,6-*O*-tri-*O*-benzyl-α-D-mannopyranoside (**7b**; 44.6 mg, 0.12 mmol). Silica gel chromatography (hexane/EtOAc, 9:1) provided **12b** (50 mg, 90%). ^{1}H NMR (300 MHz) δ: 8.08–8.06 (m, 2H), 8.05 (m, 1H), 7.56–7.19 (m, 17H), 5.75 (dd, J = 49.3, 1.7 Hz, 1H), 5.74 (t, J = 2.4 Hz, 1H), 4.89 (d, J = 10.5 Hz, 1H), 4.81 (d, J = 11.1 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.21–3.96 (m, 3H), 3.91 (dd, J = 11.2, 3.6 Hz, 1H), 3.80 (dd, J = 11.2, 1.5 Hz, 1H). ^{13}C NMR (75 MHz) δ: 165.3, 138.1, 138.0, 137.5, 133.4, 129.9 (×2), 128.5 (×2), 128.4 (×5), 128.3 (×3), 128.0 (×2), 127.9 (×2), 127.8, 127.7, 127.5 (×2), 105.5 (d, J = 219.3 Hz), 77.2, 75.3, 73.9 (d, J = 2.5 Hz), 73.4, 73.2, 71.8, 68.3, 67.2 (d, J = 40.0 Hz). API-ES positive: 579 $(M + Na)^+$. Anal. calcd for $C_{34}H_{33}O_6F$ (556.23): C 73.36, H 5.98; found: C 73.54, H 5.86.

2,3,4,6-Tetra-O-benzoyl-α-D-mannopyranosyl fluoride (13)

A solution of IPy_2BF_4 (55.8 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was cooled to −78 °C and HBF_4 (16 μL, 0.15 mmol) was added. After 5 min of stirring, a solution of *n*-pentenyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (**8**; 66.4 mg, 0.1 mmol) in dry CH_2Cl_2 (3 mL) was added. The stirring was maintained at −78 °C for 30 min before $BF_3{\cdot}OEt_2$ (13 μL, 0.1 mmol) was added. The reaction mixture was then warmed to room temperature over 20 min and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated sodium bicarbonate, and water. The organic layer was then dried and concentrated and the residue was purified by flash chromatography (hexane/EtOAc, 8:2) to provide pure **13** (45 mg, 75%). $[\alpha]_D$ −29.7 (*c* 1.6, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.14–7.26 (m, 20H), 6.22 (t, J = 10.1 Hz, 1H), 5.96–5.86 (m, 2H), 5.86 (dd, $J_{1,2}$ = 43.1, 1.8 Hz, 1H), 4.79 (dd, J = 12.3, 2.2 Hz, 1H), 4.61 (m, 1H), 4.49 (dd, J = 12.3, 3.8 Hz, 1H). API-ES positive: 622.1 $(M + Na)^+$. Anal. calcd for $C_{34}H_{27}O_9F$ (598.57): C 68.22, H 4.55; found: C 68.14, H 4.43.

Reaction of *n*-pentenyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (14)

Application of General procedure B to partially protected NPG **14** (77.8 mg, 0.15 mmol) followed by flash chromatography (hexane/EtOAc, 8:2) afforded glycosyl fluoride **16** (28.5 mg, 42%) followed by disaccharide **17** (19.5 mg, 15%).

3,4,6-Tri-O-benzyl-α-D-mannopyranosyl fluoride (16)

$[\alpha]_D$ +9.3 (*c* 1.3, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 7.29–7.29 (m, 15H), 5.59 (dd, J = 49.4, 1.6 Hz, 1H), 4.75 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 10.8 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 4.03 (m, 1H), 3.91–3.78 (m, 3H), 3.70 (dd, J = 10.9, 3.4 Hz, 1H), 3.62 (dd, J = 10.9, 1.4 Hz, 1H). ^{13}C NMR (100 MHz) δ: 138.0, 137.9, 137.5, 128.6 (×2), 128.4 (×2), 128.3 (×2), 128.1, 127.9 (×2), 127.88 (×2), 127.85 (×2), 127.7, 127.6, 107.2 (d, J = 217.3 Hz), 79.0 (d, J = 1.8 Hz), 75.2, 73.5, 73.3 (d, J = 2.9 Hz), 73.2, 72.4, 68.2, 67.1 (d, J = 39.7 Hz). ^{19}F NMR (376 MHz) δ: −141.0 (d, J = 49.4 Hz). API-ES positive: 475.1 $(M + Na)^+$. Anal. calcd for $C_{27}H_{29}O_5F$ (452.51): C 71.66, H 6.46; found: C 71.54, H 6.34.

3,4,6-Tri-O-benzyl-2-O-(3,4,6-tri-O-benzyl-D-mannopyranosyl)-α-D-mannopyranosyl fluoride (17)

$[\alpha]_{Hg}$ (435 nm) +38.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.25–7.08 (m, 30H), 5.63 (dd, J = 50.4, 1.3 Hz, 1H), 5.05 (bs, 1H), 4.87–4.48 (m, 14H), 4.11 (m, 2H), 3.91–3.72 (m, 8H). Anal. calcd for $C_{54}H_{57}O_{10}F$ (884.39): C 73.28, H 6.49; found: C 73.14, H 6.34.

Reaction of *n*-pentenyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranose (15)

Application of General procedure B to partially protected NPG **15** (77.8 mg, 0.15 mmol) followed by flash chromatography (hexane/EtOAc, 8:2) afforded glycosyl fluoride **18** (27 mg, 40%) followed by disaccharide **19** (20 mg, 15%). When NPG **15** (38.9 mg, 0.075 mmol) was subjected to the General procedure C with 10 equiv of HF–pyridine followed by flash chromatography (hexane/EtOAc, 8:2), glycosyl fluoride **18** was exclusively obtained (32 mg, 94%).

3,4,6-Tri-O-benzyl-α-D-glucopyranosyl fluoride (18)

$[\alpha]_D$ +71.3 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.28–7.08 (m, 15H), 5.54 (dd, J = 53.8, 2.3 Hz, 1H), 4.84 (d, J = 11.3 Hz, 1H), 4.75 (d, J = 11.1 Hz, 2H), 4.55 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 3.98 (m, 1H), 3.81–3.76 (m, 4H), 3.70 (dd, J = 10.8, 1.8 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.2, 137.8, 137.6, 128.5 (×2), 128.4 (×3), 127.9 (×3), 127.84 (×3), 127.81 (×3), 127.7, 107.1 (d, J = 224.0 Hz), 81.9, 76.6, 75.4, 74.9, 73.5, 73.0 (d, J = 3.4 Hz), 72.3 (d, J = 25.6 Hz), 67.7. ^{19}F NMR (376 MHz) δ: −151.2 (dd, J = 53.8, 24.6 Hz). API-ES positive: 475.1 $(M + Na)^+$. Anal. calcd for $C_{27}H_{29}O_5F$ (452.51): C 71.66, H 6.46; found: C 71.60, H 6.48.

3,4,6-Tri-O-benzyl-2-O-(3,4,6-tri-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranosyl fluoride (19)

^{1}H NMR (300 MHz) δ: 7.37–7.07 (m, 30H), 5.76 (dd, J = 53.5, 1.5 Hz, 1H), 5.07 (d, J = 2.1 Hz, 1H), 4.93 (d, J = 11.2 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.84 (d, J = 10.7 Hz, 1H), 4.83 (d, J = 10.4 Hz, 1H), 4.82 (d, J = 10.9 Hz, 1H), 4.76 (d, J = 10.5 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 10.7 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 10.9 Hz, 1H), 4.34 (d, J = 12.1 Hz, 1H), 3.97–3.90 (m, 3H), 3.84–3.68 (m, 7H), 3.47 (dd, J = 11.1, 2.8 Hz, 1H), 3.40 (dd, J = 10.7, 1.2 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.5, 138.4, 137.9, 137.8, 137.6 (×2), 128.5 (×4), 128.4 (×2), 128.3 (×2), 128.3 (×2), 128.2 (×2), 128.1 (×2), 128.0 (×2), 127.9 (×4), 127.8, 127.8, 127.7 (×2), 127.7 (×2), 127.6 (×2), 127.6, 127.5, 104.1 (d, J = 226.6 Hz), 96.5, 82.9, 79.8, 77.1, 76.1, 75.2, 75.1, 74.9 (d, J = 26.5 Hz), 74.8, 73.5, 73.3, 72.9 (d, J = 3.6 Hz), 72.6, 70.8, 67.8, 67.7. API-ES positive: 886.3 $(M + H)^+$. Anal. calcd for $C_{54}H_{57}O_{10}F$ (884.39): C 73.28, H 6.49; found: C 73.2, H 6.48.

4-Fluor-5-iodo-pentyl 3,4,6-tri-O-benzyl-α-D-mannopyranoside (20)

Mixture of diastereomers (1:1). ^{1}H NMR (300 MHz) δ: 7.30–7.08 (m, 15H), 4.82 (d, J = 1.5 Hz, 1H), 4.75 (d, J =

10.8 Hz, 1H), 4.65 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 10.8 Hz, 1H), 4.39 (m, 1H), 3.94 (m, 1H), 3.82−3.61 (m, 5H), 3.42− 3.34 (m, 1H), 3.24 (d, J = 5.4 Hz, 1H), 3.18 (d, J = 5.4 Hz, 1H), 1.85−1.52 (m, 4H). ^{13}C NMR (75 MHz) δ: 138.4 (×2), 138.1, 128.8 (×2), 128.6 (×2), 128.5 (×2), 128.2 (×2), 128.1 (×2), 128.0 (×3), 127.9, 127.8, 99.5, 99.4, 93.3, 90.9, 80.4, 75.4, 74.5, 73.7, 72.3, 71.4, 69.2, 68.6, 67.2, 32.0, 31.7, 25.0, 6.9, 6.6. Anal. calcd for $C_{32}H_{38}O_6FI$ (664.54): C 57.84, H 5.76; found: C 57.73, H 7.64.

n-*Pentenyl 2,3,4-tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (24a)*

To a stirred solution of fluoride **12a** (54.2 mg, 0.1 mmol), NPG **21** (29 mg, 0.1 mmol), and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (5 mL) was added ytterbium(III) trifluoromethanesulfonate (62 mg, 0.1 mmol). Stirring was maintained for 10 min, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 7:3) to give disaccharide **24a** (55.2 mg, 68%). $[\alpha]_D$ +37.6 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.32−7.06 (m, 20H), 5.71 (ddt, J = 17.1, 10.4, 6.6 Hz, 1H), 5.04 (s, 2H), 4.86−4.96 (m, 1H), 4.81 (d, J = 10.9 Hz, 1H), 4.73 (bs, 1H), 4.65 (s, 2H), 4.61 (d, J = 12.2 Hz, 1H), 4.53 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.43 (d, J = 10.9 Hz, 1H), 3.85−3.26 (m, 14H), 3.42 (s, 3H), 3.41 (s, 3H), 3.36 (s, 3H), 2.06−1.97 (m, 2H), 1.61−1.52 (m, 2H). ^{13}C NMR (75 MHz) δ: 138.7, 138.6, 138.5, 138.4, 137.9, 128.3 (×2), 128.2 (×6), 127.8 (×2), 127.7 (×2), 127.6 (×2), 127.5 (×2), 127.4 (×2), 127.3 (×2), 114.9, 98.0, 96.6, 81.4, 79.9, 77.1, 76.1, 74.9, 74.8 (×2), 73.2, 72.3, 71.8, 71.7, 71.4, 69.2, 66.9, 65.9, 60.8, 58.8, 57.6, 30.3, 28.5. API-ES positive: 830.5 $(M + NH_4)^+$, 835.2 $(M + Na)^+$, 859.5 $(M + 2Na)^+$. Anal. calcd for $C_{48}H_{60}O_{11}$ (812.98): C 70.91, H 7.44; found: C 71.06, H 7.37.

n-*Pentenyl 2,3,4-tri*-O-*methyl-6*-O-*(2*-O-*benzoyl-,3,4,6-tri*-O-*benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (24b)*

To a stirred solution of fluoride **12b** (27.8 mg, 0.05 mmol), NPG **21** (14.5 mg, 0.05 mmol), and 4 Å molecular sieves (25 mg) in CH_2Cl_2 (3 mL) was added ytterbium(III) trifluoromethanesulfonate (62 mg, 0.1 mmol). Stirring was maintained for 10 min, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 7:3) to give disaccharide **24b** (31 mg, 75%). $[\alpha]_D$ +13.2 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.09−8.06 (m, 2H), 7.57−7.17 (m, 18H), 5.80 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.73 (m, 1H), 5.09 (d, J = 1.8 Hz, 1H), 5.05−4.95 (m, 2H), 4.88 (d, J = 1.5 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 12.3 Hz, 1H), 4.76 (d, J = 12.9 Hz, 1H), 4.54 (m, 3H), 4.12−4.10 (m, 1H), 3.96 (m, 1H), 3.91 (dd, J = 10.8, 3.6 Hz, 1H), 3.81−3.57 (m, 8H), 3.51 (s, 6H), 3.51 (s, 3H), 3.46−3.37 (m, 2H). ^{13}C NMR (75 MHz) δ: 165.4, 138.6, 138.5, 138.0, 137.9, 132.9, 130.0, 129.9 (×3), 128.3 (×2), 128.29 (×2), 128.24 (×2), 128.21 (×2), 128.1 (×2), 127.8 (×2), 127.6, 127.5 (×2), 127.4, 114.9, 98.1, 96.5, 81.4, 78.3, 76.3, 75.1, 74.2, 73.3, 71.5, 71.4, 71.0, 69.0, 68.7, 67.0, 66.7, 60.8, 58.8, 57.5, 30.3, 28.6. API-ES positive: 844.3 $(M + NH_4)^+$, 872 $(M + 2Na)^+$. Anal. calcd for $C_{48}H_{58}O_{12}$ (826.39): C 69.71, H 7.07; found: C 69.61, H 6.94.

2,3,4-Tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzyl-D-glucopyranosyl)-α- and -β-D-glucopyranosyl fluoride (25)

To a stirred solution of pentenyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**; 122 mg, 0.2 mmol) and 2,3,4-tri-*O*-methyl-α-D-glucopyranosyl fluoride (**22**; 34.8 mg, 0.15 mmol) in CH_2Cl_2 (6 mL) under argon was added IDCP (234 mg, 0.5 mmol) in one portion. The solution was stirred for 2 h and then the mixture was quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 8:2 to 1:1) gave disaccharide **25*α*** (51 mg, 45%) followed by disaccharide **25*β*** (50 mg, 45%). α-Anomer: $[\alpha]_D$ +37.5 (*c* 0.35, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.30−7.05 (m, 20H), 5.48 (dd, J = 53.3, 2.7 Hz, 1H), 4.98 (d, J = 17.4 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 16.7 Hz, 1H), 4.61 (d, J = 17.2 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.42 (bs, 1H), 4.40 (d, J = 12.1 Hz, 1H), 3.91 (t, J = 9.2 Hz, 1H), 3.80−3.39 (m, 9H), 3.56 (s, 3H), 3.48 (s, 3H), 3.38 (s, 3H), 3.24 (t, J = 9.5 Hz, 1H), 2.93 (ddd, J = 25.7, 9.5, 2.7 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.8, 138.5, 138.2, 137.9, 128.3 (×5), 127.9 (×3), 127.8 (×3), 127.7 (×3), 127.6 (×2), 127.5 (×2), 127.3 (×2), 104.9 (d, J = 226.3 Hz), 94.4, 82.9, 81.8, 81.2 (d, J = 24.8 Hz), 80.1, 78.4, 77.5, 75.6, 75.1, 73.4, 72.3, 72.4 (d, J = 3.5 Hz), 70.3, 68.4, 66.0, 60.8, 60.6, 59.1. API-ES positive: 764.3 $(M + NH_4)^+$, 769.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{51}FO_{10}$ (746.86): C 69.15, H 6.88; found: C 69.35, H 6.65. β-Anomer: $[\alpha]_D$ +17.5 (*c* 0.45, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.29−7.08 (m, 20H), 5.60 (dd, J = 53.3, 2.6 Hz, 1H), 4.90 (d, J = 11.0 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.72 (d, J = 9.3 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 4.47 (d, J = 10.8 Hz, 1H), 4.37 (d, J = 7.7 Hz, 1H), 4.13 (dd, J = 11.0, 1.7 Hz, 1H), 3.83 (ddd, J = 10.0, 4.5, 1.6 Hz, 1H), 3.70−3.40 (m, 8H), 3.56 (s, 3H), 3.47 (s, 3H), 3.39 (s, 3H), 3.18 (t, J = 9.6 Hz, 1H), 3.11 (ddd, J = 25.7, 9.6, 2.7 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.5, 138.3, 138.1, 137.9, 128.4 (×2), 128.33 (×2), 128.32 (×2), 128.31 (×2), 128.0 (×2), 127.9 (×2), 127.8 (×2), 127.7, 127.6 (×2), 127.57, 127.56, 127.55, 104.8 (d, J = 226.4 Hz), 103.7, 84.8, 82.8, 81.9, 81.3 (d, J = 24.8 Hz), 78.5, 77.8, 75.7, 75.0, 74.9, 74.8, 73.4, 72.2 (d, J = 3.9 Hz), 68.9, 68.1, 60.9, 60.5, 59.1. API-ES positive: 769.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{51}FO_{10}$ (746.86): C 69.15, H 6.88; found: C 69.3, H 6.93.

2,3,4-Tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*methyl-D-mannopyranosyl)-α- and -β-D-mannopyranosyl fluoride (26a)

To a stirred solution of fluoride **23** (22 mg, 0.1 mmol), NPG **6a** (30 mg, 0.1 mmol), and 4 Å molecular sieves (25 mg) in CH_2Cl_2 (3 mL) was added $I(coll)_2ClO_4$ (117 mg, 0.25 mmol). Stirring was maintained for 1 h, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated aqueous sodium bicarbonate, and water. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 2:8)

to give disaccharide **26aα** (20 mg, 44%) followed by disaccharide **26aβ** (19 mg, 44%). α-Anomer: $[\alpha]_D$ +26.8 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 5.65 (dd, *J* = 50.4, 2.1 Hz, 1H), 5.03 (d, *J* = 1.8 Hz, 1H), 3.91 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.74−3.70 (m, 2H), 3.67−3.65 (m, 3H), 3.61 (m, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.52 (s, 3H), 3.49 (s, 3H), 3.46 (s, 3H), 3.40 (s, 3H), 3.58−3.44 (m, 6H). ^{13}C NMR (75 MHz) δ: 105.4 (d, *J* = 221.3 Hz), 97.3, 81.1, 80.6 (d, *J* = 1.6 Hz), 76.8, 76.3, 75.7 (d, *J* = 34.1 Hz), 75.1, 73.7 (d, *J* = 2.2 Hz), 71.6, 71.3, 65.9, 60.9, 60.6, 59.4, 59.2, 58.8, 57.9, 57.7. API-ES positive: 465.2 $(M + Na)^+$. Anal. calcd for $C_{19}H_{35}FO_{10}$ (442.47): C 51.57, H 7.97; found: C 51.64, H 8.03. β-Anomer: $[\alpha]_D$ −20.1 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 5.66 (dd, *J* = 50.4, 1.8 Hz, 1H), 4.48 (bs, 1H), 4.22 (dd, *J* = 11.1, 1.5 Hz, 1H), 3.87−3.82 (m, 1H), 3.73−3.70 (m, 2H), 3.65 (s, 3H), 3.52 (s, 3H), 3.51 (s, 6H), 3.49 (s, 3H), 3.48 (s, 3H), 3.41 (s, 3H), 3.67−3.25 (m, H), 3.18 (dd, *J* = 8.7, 3.3 Hz, 1H). API-ES positive: 465.2 $(M + Na)^+$. Anal. calcd for $C_{19}H_{35}FO_{10}$ (442.47): C 51.57, H 7.97; found: C 51.39, H 8.15.

6-O-tert-*Butyldiphenylsilyl-2,3,4-tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*methyl-*D *mannopyranosyl-α- and -β-*D*-mannopyranosyl fluoride (26b)*

To a stirred solution of fluoride **23** (22 mg, 0.1 mmol), NPG **6b** (52.8 mg, 0.1 mmol), and 4 Å molecular sieves (25 mg) in CH_2Cl_2 (3 mL) was added $I(coll)_2ClO_4$ (117 mg, 0.25 mmol). Stirring was maintained for 1 h, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated aqueous sodium bicarbonate, and water. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/AcOEt, 1:1) to give disaccharide **26bα** (32 mg, 48%) followed by disaccharide **26bβ** (16 mg, 24%). α-Anomer: $[\alpha]_D$ +43.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.76−7.71 (m, 4H), 7.42−7.34 (m, 6H), 5.66 (dd, *J* = 50.4, 1.5 Hz, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 3.95−3.83 (m, 4H), 3.76−3.66 (m, 4H), 3.57−3.46 (m, H), 3.53 (s, 6H), 3.51 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (75 MHz) δ: 135.9 (×2), 135.6 (×2), 134.1, 133.6, 129.4 (×2), 127.5 (×2), 127.4 (×2), 105.4 (d, *J* = 220.9 Hz), 96.8, 81.2, 80.5 (d, *J* = 1.6 Hz), 76.7, 76.1, 75.6 (d, *J* = 34.0 Hz), 75.2, 73.8 (d, *J* = 2.0 Hz), 73.0, 65.5, 63.3, 60.9, 60.6, 59.3, 58.3, 57.9, 57.6, 26.7 (×3), 19.4. API-ES positive: 684.3 $(M + NH_4)^+$. Anal. calcd for $C_{34}H_{51}FO_{10}Si$ (666.85): C 61.24, H 7.71; found: C 61.09, H 7.65. β-Anomer: $[\alpha]_D$ −9.5 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.78−7.70 (m, 4H), 7.42− 7.35 (m, 6H), 5.69 (dd, *J* = 50.4, 1.8 Hz, 1H) 4.48 (bs, 1H), 4.25 (dd, *J* = 11.1, 1.8 Hz, 1H), 3.95 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.91−3.85 (m, 1H), 3.76 (d, *J* = 3.3 Hz, 1H), 3.72 (m, 1H), 3.65 (s, 3H), 3.62−3.55 (m, 1H), 3.53 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 3.48 (s, 6H), 3.44 (t, *J* = 9.3 Hz, 1H), 3.25−3.22 (m, 1H), 3.19 (dd, *J* = 9.3, 3.0 Hz, 1H), 1.05 (s, 9H). API-ES positive: 684.3 $(M + NH_4)^+$. Anal. calcd for $C_{34}H_{51}FO_{10}Si$ (666.85): C 61.24, H 7.71; found: C 61.15, H 7.84.

2,3,4-Tri-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzoyl-α-*D*-mannopyranosyl)-α-*D*-glucopyranosyl fluoride (27)*

A solution of *n*-pentenyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (**8**; 79.7 mg, 0.12 mmol), 2,3,4-tri-*O*-methyl-α-D-mannopyranosyl fluoride (**23**; 22.4 mg, 0.1 mmol), NIS (44.8 mg, 0.2 mmol), and 4 Å molecular sieves (25 mg) in anhydrous CH_2Cl_2 (3 mL) was stirred under argon for 10 min at room temperature. Then the reaction was cooled to −30 °C and BF_3OEt_2 (15 μL, 0.12 mmol) was added. After 30 min, the reaction was diluted with CH_2Cl_2 (10 mL), washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The obtained residue was a complex mixture of compounds from which disaccharide **27** could be purified by flash chromatography (hexane/AcOEt, 7:3; 20 mg, 25%). $[\alpha]_D$ −2.3 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.0−7.15 (m, 20H), 6.04 (t, *J* = 10.0 Hz, 1H), 5.87 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.70 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.64 (dd, *J* = 50.3, 1.8 Hz, 1H), 5.14 (d, *J* = 1.6 Hz, 1H), 4.67−4.58 (m, 1H), 4.47−4.39 (m, 2H), 3.96 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.87−3.78 (m, 2H), 3.67 (m, 1H), 3.54 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.53−3.42 (m, 2H). ^{13}C NMR (75 MHz) δ: 166.2, 165.4 165.3, 165.2, 133.4 (×2), 133.1, 133.0, 129.9, 129.8 (×4), 129.7 (×2), 129.6 (×2), 129.4, 129.1, 128.9, 128.5 (×2), 128.4 (×2), 128.3 (×2), 128.2 (×2), 105.3 (d, *J* = 220.8 Hz), 98.0, 80.5, 75.5 (d, *J* = 34.0 Hz), 75.4, 73.7, 70.3, 69.9, 68.8, 67.1, 66.9, 62.8, 60.9, 59.4, 57.8. API-ES positive: 825.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{43}FO_{14}$ (802.79): C 64.33, H 5.40; found: C 64.47, H 5.49.

Methyl 2,3,4-tri-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzoyl-α-*D*-mannopyranosyl)-α-*D*-glucopyranoside (29)*

A stirred solution of **28** (57.5 mg, 0.087 mmol), **16** (47 mg, 0.087 mmol), and **2** (20 mg, 0.087 mmol) in CH_2Cl_2 (4 mL) under argon was cooled to −30 °C and then NIS (38.7 mg, 0.173 mmol) and $BF_3{\cdot}OEt_2$ (1.1 μL, 0.0087 mmol) were added. The solution was stirred for 20 min and then quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 3:2 to 1:1) gave recovered **16** (40 mg, 85%) and disaccharide **29** (68 mg, 96%). $[\alpha]_D$ +4.3 (*c* 3.2, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.05−7.17 (m, 20H), 6.02 (t, *J* = 10.0 Hz, 1H), 5.85 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.67 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.14 (d, *J* = 1.4 Hz, 1H), 4.74 (d, *J* = 3.5 Hz, 1H), 4.68 (dd, *J* = 11.9, 2.0 Hz, 1H), 4.48 (ddd, *J* = 9.9, 4.3, 2.0 Hz, 1H), 4.39 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.91 (dd, *J* = 11.0 Hz, 5.4 Hz, 1H), 3.79 (dd, *J* = 10.9, 1.4 Hz, 1H), 3.69−3.63 (m, 1H), 3.57 (s, 3H), 3.53 (s, 3H), 3.49 (m, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 3.11 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.05 (m, 1H). ^{13}C NMR (75 MHz) δ: 166.4, 165.7, 165.6, 165.5, 133.7 (×2), 133.4, 133.3, 130.2, 130.1 (×2), 129.9 (×6), 129.6 (×2), 129.3 (×4), 129.2 (×2), 128.8, 128.7, 128.6, 97.7, 97.5, 83.8, 82.0, 79.8, 70.6, 70.2, 70.0, 69.2, 67.2, 66.8, 63.1, 61.1, 60.8, 59.3, 55.4. API-ES positive: 837.2 $(M + Na)^+$. Anal. calcd for $C_{44}H_{46}O_{15}$ (814.83): C 64.86, H 5.69; found: C 65.02, H 5.73.

2,3,4-Tri-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzoyl-α-*D*-mannopyranosyl)-α-*D*-glucopyranosyl fluoride (31)*

A stirred solution of NPOE **28** (66.4 mg, 0.1 mmol) and fluoride **23** (22.4 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) under argon was cooled to −20 °C and then NIS (44.8 mg, 0.2 mmol) and $Yb(OTf)_3$ (62 mg, 0.1 mmol) were added. The solution was stirred for 1 h and then quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was

dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 3:2 to 1:1) gave disaccharide **31** (75 mg, 94%). $[\alpha]_D$ −2.3 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.0−7.15 (m, 20H), 6.04 (t, *J* = 10.0 Hz, 1H), 5.87 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.70 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.64 (dd, *J* = 50.3, 1.8 Hz, 1H), 5.14 (d, *J* = 1.6 Hz, 1H), 4.67−4.58 (m, 1H), 4.47−4.39 (m, 2H), 3.96 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.87−3.78 (m, 2H), 3.67 (m, 1H), 3.54 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.53−3.42 (m, 2H). ^{13}C NMR (75 MHz) δ: 166.2, 165.4, 165.3, 165.2, 133.4 (×2), 133.1, 133.0, 129.9, 129.8 (×4), 129.7 (×2), 129.6 (×2), 129.4, 129.1, 128.9, 128.5 (×2), 128.4 (×2), 128.3 (×2), 128.2 (×2), 105.3 (d, *J* = 220.8 Hz), 98.0, 80.5, 75.5 (d, *J* = 34.0 Hz), 75.4, 73.7, 70.3, 69.9, 68.8, 67.1, 66.9, 62.8, 60.9, 59.4, 57.8. API-ES positive: 825.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{43}FO_{14}$ (802.79): C 64.33, H 5.40; found: C 64.47, H 5.49.

One-pot assembly of trisaccharide 32

A mixture of NPOE **28** (73 mg, 0.11 mmol), 2,3,4-tri-*O*-methyl-α-D-mannopyranosyl fluoride (**23**; 22.4 mg, 0.1 mmol), and 4 Å molecular sieves in CH_2Cl_2 (4 mL) was stirred under argon at −20 °C for 10 min. Then NIS (24.6 mg, 0.11 mmol) and $Yb(OTf)_3$ (68.2 mg, 0.11 mmol) were added. The reaction mixture was stirred at −20 °C for 1 h, after which *n*-pentenyl-2,3,4-tri-*O*-methyl-α-D-mannopyranoside (**21**; 26.1 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was allowed to warm to room temperature and then $Yb(OTf)_3$ (68.2 mg, 0.11 mmol) was added. Upon stirring for 10 min, the reaction was quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 1:1) gave trisaccharide **32** (69 mg, 72%). $[\alpha]_D$ −2.3 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.31−7.79 (m, 8H), 7.61−7.22 (m, 12H), 6.10 (t, *J* = 9.9 Hz, 1H), 5.96 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.77 (ddt, *J* = 17.1, 10.5, 6.6 Hz, 1H), 5.76 (m, 1H), 5.26 (d, *J* = 1.8 Hz, 1H), 5.12 (d, *J* = 1.0 Hz, 1H), 5.03−4.92 (m, 2H), 4.88 (bs, 1H), 4.71−4.68 (m, 1H), 4.57−4.47 (m, 2H), 4.05−3.97 (m, 2H), 3.91−3.87 (m, 1H), 3.81−3.35(m, 11H), 3.58 (s, 3H), 3.56 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H), 2.11−2.04 (m, 2H), 1.69−1.60 (m, 2H). ^{13}C NMR (75 MHz) δ: 166.2, 165.4, 165.2, 165.1, 137.9, 133.3, 133.2, 132.9, 129.9, 129.8 (×2), 129.77 (×2), 129.73 (×2) 129.6 (×2), 129.5, 129.2, 129.0, 128.5 (×2), 128.4 (×2), 128.3 (×2), 128.2 (×2), 114.9, 97.6, 96.9, 96.6, 81.39, 81.38, 77.1, 76.6, 76.3, 75.8, 71.4, 71.1, 70.4, 69.9, 68.7, 67.1, 67.0 (×2), 66.0, 62.9, 60.8, 60.7, 58.7, 58.6, 57.5, 57.4, 30.3, 28.6. API-ES positive: 1090.3 $(M + NH_4)^+$, 1095.4 $(M + Na)^+$. Anal. calcd for $C_{57}H_{68}O_{20}$ (1073.14): C 63.80, H 6.39; found: C 63.93, H 6.51.

One-pot assembly of tetrasaccharide 34

A mixture of NPOE **28** (88.4 mg, 0.133 mmol), 2,3,4-tri-*O*-methyl-α-D-mannopyranosyl fluoride (**23**; 27.1 mg, 0.12 mmol), and 4 Å molecular sieves in CH_2Cl_2 (4 mL) was stirred under argon at −20 °C for 10 min. Then NIS (29.8 mg, 0.133 mmol) and $Yb(OTf)_3$ (82.5 mg, 0.133 mmol) were added. The reaction mixture was stirred at −20 °C for 1 h, after which *n*-pentenyl-2,3,4-tri-*O*-methyl-α-D-mannopyranoside (**21**;31.9 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added. The reaction was allowed to warm to room temperature and then $Yb(OTf)_3$ (41.2 mg, 0.066 mmol) was added. Upon stirring for 30 min, the acceptor **33** (32 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added and the reaction was cooled to −30 °C. Then NIS (24.6 mg, 0.11 mmol) and $BF_3(OEt)_2$ (3.8 μL, 0.03 mmol) were added. After 12 h, the reaction was quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 2:8) yielded tetrasaccharide **34** (32.6 mg, 25%). Major isomer, selected signals: ^{1}H NMR (300 MHz) δ: 5.25 (d, *J* = 1.8 Hz, 1H), 5.11 (d, *J* = 1.8 Hz, 1H), 4.93 (d, *J* = 2.5 Hz, 1H), 4.91 (bs, 1H), 3.58 (s, 3H), 3.54 (s, 3H), 3.50 (s, 6H), 3.47 (s, 3H), 3.44 (s, 3H), 3.35 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75 MHz) δ: 97.7, 96.9, 96.8, 96.6. Electrospray ionization (ESI)-HR-MS: 1324.5055 $(M + NH_4)^+$, 1329.4602 $(M + Na)^+$. Anal. calcd for $C_{65}H_{78}O_{28}$ (1306.46): C 59.72, H 6.01, O 34.27; found: C 59.88, H 6.09.

Methyl 3,5-di-O-benzyl-2-O-benzoyl-β-D-ribofuranoside (35)

To a solution of 1,2-orthoester **36** (80 mg, 0.18 mmol) in dry CH_2Cl_2 (3 mL) at −40 °C under argon was added a solution of HF–pyridine (10.27 mL, 1.78 mmol) in dry CH_2Cl_2 (2 mL). After 10 min, when all the starting material had disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched by saturated aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc, 8:2) to yield fluoride **37** (33 mg, 42%) followed by methyl glycoside **35** (19 mg, 24%). For **35**: $[\alpha]_D$ +32.0 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.10−8.07 (m, 3H), 7.61−7.23 (m, 12H), 5.45 (d, *J* = 4.3 Hz, 1H), 5.04 (s, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.36 (m, 1H), 4.24 (m, 1H), 3.61 (ddd, *J* = 16.6, 10.5, 4.6 Hz, 2H), 3.38 (s, 3H, OMe). ^{13}C NMR (75 MHz) δ: 165.6, 138.2, 137.4, 133.3, 129.9 (×2), 129.6, 128.4 (×2), 128.3 (×4), 128.0 (×2), 127.8, 127.6 (x 2), 127.5, 106.3, 80.5, 77.9, 74.2, 73.2, 73.0, 71.2, 55.1. API-ES positive: 471.5 $(M + Na)^+$.

3,5-Di-O-benzyl-2-O-benzoyl-β-D-ribofuranosyl fluoride (37)

Following General procedure D, a solution of HF–pyridine (40 equiv, 6 mmol, 0.9 mL) was treated with orthoester **36** (70 mg, 0.16 mmol) to afford, after flash chromatography (hexane/EtOAc, 9:1), compound **37** (72 mg, quantitative yield) as a colorless oil. $[\alpha]_D$ +44.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.10−8.07 (m, 3H), 7.61−7.23 (m, 12H), 5.85 (d, *J* = 61.9 Hz, 1H), 5.60 (t, *J* = 4.0 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.48−4.40 (m, 1H), 4.35−4.30 (m, 1H), 3.74 (dd, *J* = 11.0, 3.2 Hz, 1H), 3.60 (dd, *J* = 11.0, 5.4 Hz, 1H). ^{13}C NMR (75 MHz) δ: 165.5, 134.0, 133.9, 133.5 (×2), 130.1 (×2), 130.0 (×4), 128.8 (×2), 128.7 (×2), 128.6 (×2), 112.6 (d, *J* = 225.2 Hz, C-1), 82.8 (d, *J* = 2.3 Hz, C-3), 75.1, 74.6, 71.2, 64.2, 29.9. ^{19}F NMR (376 MHz) δ: 115.1 (m). API-ES positive: 459.2 $(M + Na)^+$. Anal. calcd for $C_{26}H_{25}FO_5$ (436.47): C 71.55, H 5.77; found: C 71.43, H 5.64.

***2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl fluoride (44)*[31]**

Following General procedure D, a solution of HF–pyridine (3.0 mmol, 0.45 mL) was treated with orthoester **38a** (80 mg, 0.15 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **12** (66 mg, 95%) as a colorless oil. In a different run, orthoester **38b** (80 mg, 0.17 mmol) was subjected to the same reaction conditions to obtain fluoride **44** (62 mg, 79%). $[\alpha]_D$ −53.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03−7.90 (m, 5H), 7.56, 7.17 (m, 10H), 5.95 (d, *J* = 58.4 Hz, 1H), 5.63 (bd, *J* = 6.1 Hz, 1H), 5.52 (m, 1H), 4.80−4.74 (m, 2H), 4.62 (dd, *J* = 12.9, 6.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6, 166.1, 165.0, 133.8, 133.7, 133.1, 129.9 (×2), 129.8 (×2), 129.7 (×2), 129.4, 128.6 (×3), 128.5 (×2), 128.4, 128.3 (×2), 112.4 (d, *J* = 226.5 Hz, C-1), 84.4, 80.8 (d, *J* = 40.0 Hz, C-2), 76.5, 63.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −124.7 (dd, *J* = 58.5, 6.0 Hz). API-ES positive: 487.3 $(M + Na)^+$. Anal. calcd for $C_{26}H_{21}FO_7$ (464.44): C 67.24, H 4.56; found: C 67.18, H 4.43.

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl fluoride (45)

Following General procedure D, a solution of HF–pyridine (3.0 mmol, 0.45 mL) was treated with orthoester **39a** (80 mg, 0.15 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **45** (70 mg, quantitative yield) as a colorless oil. In a different run, orthoester **39b** (80 mg, 0.17 mmol) was subjected to the same reaction conditions to obtain fluoride **45** (77 mg, quantitative yield). $[\alpha]_D$ +105.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10−7.87 (m, 5H), 7.63−7.31 (m, 10H), 5.98 (d, *J* = 61.0 Hz, 1H), 5.93−5.86 (m, 2H), 4.87 (m, 1H), 4.78 (dd, *J* = 12.1, 3.8 Hz, 1H), 4.59 (dd, *J* = 12.1, 5.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.4, 165.5, 165.2, 134.0, 133.9, 133.5, 130.1 (×2), 130.4 (×2), 130.2 (×2), 129.7, 128.9, 128.8 (×3), 128.7 (×2), 128.6 (×2), 112.3 (d, *J* = 226.3 Hz, C-1), 81.1 (d, *J* = 2.7 Hz, C-3), 74.9 (d, *J* = 36.2 Hz, C-2), 71.2, 64.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −116.0 (bd, *J* = 65.0 Hz). API-ES positive: 487.3 $(M + Na)^+$. Anal. calcd for $C_{26}H_{21}FO_7$ (464.44): C 67.24, H 4.56; found: C 67.13, H 4.49.

3,5-Di-O-benzyl-2-O-benzoyl-α-D-arabinofuranosyl fluoride (46)

Following General procedure D, a solution of HF–pyridine (3.6 mmol, 0.53 mL) was treated with orthoester **40a** (60 mg, 0.12 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **46** (51 mg, 91%) as a colorless oil. In a different run, orthoester **40b** (40 mg, 0.09 mmol) was subjected to the same reaction conditions to obtain fluoride **46** (39 mg, 93%). $[\alpha]_D$ +14.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.98−7.95 (m, 3H), 7.64−7.28 (m, 12H), 5.90 (d, *J* = 59.0 Hz, 1H, 1-H), 5.54 (dd, *J* = 7.1, 1.1 Hz, 1H, 2-H), 4.84 (d, *J* = 12.3 Hz, 1H, –OCH_2Ph), 4.65 (d, *J* = 12.3 Hz, 1H, –OCH_2Ph), 4.61−4.58 (m, 1H, 4-H), 4.12 (dd, *J* = 4.6, 1.1 Hz, 1H, 3-H) 3.68 (dd, *J* = 10.8, 4.5 Hz, 1H, 5a-H), 3.62 (dd, *J* = 10.8, 6.0 Hz, 1H, 5b-H). ^{13}C NMR (75 MHz) δ: 165.4, 137.9, 137.5, 133.9, 130.1 (×2), 129.2, 128.8 (×2) 128.7 (×2), 128.6 (×2), 128.2 (×3), 128.0, 127.9 (×2), 113.2 (d, *J* = 225.4 Hz, 1-C), 85.4, 82.3, 80.7 (d, *J* = 39.2 Hz, 2-C), 73.7, 72.6, 69.1. ^{19}F NMR (376 MHz) δ: −123.5 (dd, *J* = 59.1, 7.0 Hz). API-ES positive: 459.2 $(M + Na)^+$. Anal. calcd for $C_{26}H_{25}FO_5$ (436.47): C 71.53, H 5.77; found: C 71.39, H 5.59.

2,5-Di-O-benzoy1-α-D-arabinofuranosyl fluoride (47)

Following General procedure D, a solution of HF–pyridine (3.06 mmol, 0.45 mL) was treated with orthoester **41** (34 mg, 0.09 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **47** (29 mg, 91%). $[\alpha]_D$ +52.1 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.09−8.04 (m, 4H), 7.59−7.41 (m, 6H), 6.00 (d, *J* = 60.0 Hz, 1H), 5.32 (dd, *J* = 10.9, 2.6 Hz, 1H), 4.72−4.50 (m, 3H), 4.33 (dd, *J* = 5.8, 2.6 Hz, 1H). ^{13}C NMR (75 MHz) δ: 166.8, 166.4, 134.2, 133.5, 130.1 (×2), 130.0 (×2), 129.7, 128.9 (×2), 128.8, 128.6 (×2), 113.2 (d, *J* = 223.9 Hz, C-1), 86.1 (d, *J* = 39.0 Hz, C-2), 84.3, 77.0, 63.5, 30.0. ^{19}F NMR (376 MHz) δ: −121.9 (dd, *J* = 59.8, 11.3 Hz). API-ES positive: 383.4 $(M + Na)^+$. Anal. calcd for $C_{19}H_{17}FO_6$ (360.33): C 63.33, H 4.76; found: C 63.17, H 4.51.

2,5-Di-O-benzoyl-1-β-D-ribofuranosyl fluoride (48)

Following General procedure D, a solution of HF–pyridine (1.82 mmol, 0.27 mL) was treated with orthoester **42** (57 mg, 0.15 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **48** (29 mg, 53%). $[\alpha]_D$ +30.4 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.03−8.00 (m, 2H), 7.65−7.30 (m, 8H), 6.01 (d, *J* = 59.7 Hz, 1H), 5.32 (dd, *J* = 10.9, 2.6 Hz, 1H), 4.69 (m, 2H), 4.54 (m,1H), 4.33 (dd, *J* = 5.8, 2.6 Hz, 1H). ^{13}C NMR (75 MHz) δ: 166.5, 166.2, 132.9, 132.0, 128.9 (×2), 128.7 (×2), 127.7 (×2), 127.4 (×2), 111.9 (d, *J* = 223.9 Hz, C-1), 84.8 (d, *J* = 39.0 Hz, C-2), 82.8, 75.9, 62.2, 28.7. ^{19}F NMR (376 MHz) δ: −115.7 (bd, *J* = 60.7 Hz). API-ES positive: 383.3 $(M + Na)^+$. Anal. calcd for $C_{19}H_{17}FO_6$ (360.33): C 63.33, H 4.76; found: C 63.21, H 4.63.

1,5-Anhydro-2-O-benzoyl-β-D-ribofuranose (49)

Following General procedure D, a solution of HF–pyridine (40 equiv, 8.8 mmol, 1.31 mL) was treated with orthoester **43** (60 mg, 0.22 mmol) to afford, after flash chromatography (hexane/EtOAc, 1:1), compound **49** (21 mg, 40%). $[\alpha]_D$ −27.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.09−8.04 (m, 2H), 7.63−7.44 (m, 3H), 5.35 (d, *J* = 4.6 Hz, 1H), 5.13 (s, 1H), 4.95 (m, 1H), 4.02 (m, 2H), 3.83 (m, 1H), 2.16 (d, 1H, OH). ^{13}C NMR (75 MHz) δ: 166.2, 133.6, 129.8 (×2), 129.3, 128.5 (×2), 104.5, 82.7, 77.2, 69.7, 66.6. API-ES positive: 473.3 $(2M + H)^+$, 495.3 $(2M + Na)^+$. Anal. calcd for $C_{12}H_{12}O_5$ (236.22): C 61.01, H 5.12; found: C 60.87, H 4.98.

2,5-Di-O-benzoyl-3-O-(2,3,5-tri-O-benzoyl-α-D-arabino-furanosyl)-α-D-arabinofuranosyl fluoride (50)

A stirred solution of NPOE **38a** (100 mg, 0.198 mmol) and fluoride **47** (74 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) under argon was cooled to 0 °C and then NIS (85.5 mg, 0.38 mmol) and $Yb(OTf)_3$ (58.9 mg, 0.10 mmol) were added. The solution was stirred for 1 h and then quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 8:2) gave disaccharide **50** (86 mg, 61%). $[\alpha]_D$ −6.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 8.13−7.93 (m, 10H), 7.60−7.21 (m, 15H), 6.00 (d, *J* = 58.1 Hz, 1H, 1-H), 5.72 (s, 1H, 1′-H), 5.63 (s, 1H, 2-H), 5.59 (d, *J* = 1.6 Hz, 1H, 3′-H), 5.57 (d, *J* = 6.6 Hz, 1H, 2-H), 4.78−4.53 (m, 7H). ^{13}C NMR (100 MHz) δ: 166.1, 166.0, 165.6, 165.3, 165.2, 133.7, 133.6, 133.5, 133.2, 133.1, 130.0 (×4), 129.9 (×2), 129.8, 129.7 (×2), 129.6 (×2), 129.5, 129.3, 128.9, 128.8,

128.7 (×2), 128.6 (×2), 128.5 (×2), 128.4 (×2), 128.3 (×2), 112.6 (d, J = 225.2 Hz), 105.6, 84.2, 82.2, 81.7, 81.3 (d, J = 40.2 Hz), 79.9, 77.4, 63.7, 63.0. API-ES positive: 827.5 $(M + Na)^+$. Anal. calcd for $C_{45}H_{37}O_{13}F$ (804.77): C 67.16, H 4.63; found: C 67.07, H 4.39.

***n*-Pentenyl-2,3-di-O-benzyl-5-O-[2,5-di-O-benzoyl-3-O-(2,3,5-tri-O-benzoyl-α-D-arabino-furanosyl)-α-D-arabino-furanosyl]-α-D-arabino-furanoside (52)**

To a stirred solution of fluoride **50** (8 mg, 0.01 mmol) and NPG **51** (8 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) cooled to −20 °C was added $BF_3{\cdot}Et_2O$ (0.9 μL, 0.00710 mmol). The reaction was allowed to warm to −10 °C and then stirred for an additional 4 h after which time it was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate. The organic extract was dried, filtered, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2) to give trisaccharide **52** (9 mg, 75%). $[\alpha]_D$ +22.2 (*c* 0.7, $CHCl_3$). ^{1}H NMR (500 MHz) δ: 8.13−7.93 (m, 10H), 7.60−7.15 (m, 25H), 5.75 (m, 1H), 5.72 (s, 1H, 1-H), 5.60 (d, J = 1.5 Hz, 1H, 2′-H), 5.53 (dd, J = 3.9, 0.7 Hz, 1H, 1-H), 5.45 (d, J = 1 Hz, 1H, 2″-H), 5.34 (s, 1H, 1-H), 4.98 (d, J = 1.3 Hz, 1H), 4.91 (m, 2H), 4.74−4.42 (m, 11H), 4.21 (dt, J = 6.6, 4.2 Hz, 1H, 4-H), 4.04 (dd, J = 6.6, 3.4 Hz, 1H, 3-H), 3.99 (dd, J = 3.4, 1.5 Hz, 1H, 2-H), 3.90 (dd, J = 11.2, 4.6 Hz, 1H, 5-H), 3.75 (dd, J = 11.2, 3.9 Hz, 1H), 3.68 (m, 1H), 3.34 (m, 1H), 2.06 (m, 2H), 1.60 (m, 2H). ^{13}C NMR (125 MHz) δ: 166.1 (d), 166.0, 165.6, 165.3, 165.2, 138.2, 137.9, 137.6, 133.5, 133.4, 133.3, 133.1, 132.9, 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.2, 129.1, 128.4 (×2), 128.3 (×2), 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 114.7, 106.1, 106.0, 105.0, 88.2, 83.4, 82.0, 81.9, 81.6, 81.1, 80.6, 80.0, 77.7, 77.6, 72.2, 71.9, 66.9, 66.3, 63.7, 63.2, 30.3, 28.7. HR-MS: 1205.4127 $(M + Na)^+$. Anal. calcd for $C_{69}H_{66}O_{18}$ (1182.42): C 70.04, H 5.62; found: C 69.94, H 5.49.

Acknowledgements

B.F.R. thanks the National Science Foundation (grant No. CHE 0717702) for financial support. This research has been supported with funds from the Ministerio de Ciencia e Innovación and Comunidad de Madrid (grant Nos. CTQ2009-10343 and S2009/PPQ-1752, respectively). We also thank Ms. M. Rodríguez (Instituto de Química Orgánica General (IQOG)) for skillful technical support.

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Allosteric *N*-acetamide-indole-6-carboxylic acid thumb pocket 1 inhibitors of hepatitis C virus NS5B polymerase — Acylsulfonamides and acylsulfamides as carboxylic acid replacements

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Abstract: Acylsulfonamide and acylsulfamide as surrogates for the carboxylic acid function of *N*-acetamide-indole-6-carboxylic acids were evaluated as allosteric inhibitors of hepatitis C virus (HCV) NS5B polymerase. Several analogs displayed excellent antiviral potency against both *1a* and *1b* HCV genotypes in cell-based subgenomic replicon assays. Structure–activity relationships (SAR) are discussed in the context of the crystal structure of an inhibitor − NS5B polymerase complex. Absorption, distribution, metabolism, and excretion pharmacokinetic (ADME-PK) properties of this class of inhibitors are also described.

Key words: hepatitis C virus (HCV), NS5B polymerase, allosteric inhibitors, antivirals, structure–activity relationship.

Résumé : On a évalué les acylsulfonamides et les acylsulfamides comme substituts de la fonction acide carboxylique des acides *N*-acétamide-indole-6-carboxylique comme inhibiteurs allostériques de la polymérase du virus de l'hépatite C (VHC) NS5B. Plusieurs analogues présentent des activités antivirales excellentes contre les génotypes *1a* et *1b* du VHC dans les essais de réplication sous-génomiques à base de cellules. On discute de relations structure–activité (RSA) dans le contexte de la structure cristalline d'un complexe inhibiteur – polymérase NS5B. On décrit aussi les propriétés pharmacocinétiques, telles les taux d'absorption, de distribution, de métabolisme et d'excrétion (PC-ADME), de cette classe d'inhibiteurs.

Mots-clés : virus de l'hépatite C (VHC), polymérase NS5B, inhibiteurs allostériques, antiviraux, relation structure–activité.

[Traduit par la Rédaction]

Introduction

The hepatitis C virus (HCV) is a blood-borne ribonucleic acid (RNA) virus that infects an estimated 170 million people worldwide and can cause severe liver damage such as cirrhosis and hepatocellular carcinomas.[1] Whereas the spread of this pathogen is now mostly limited to intravenous drug use and unsafe medical practice in developing countries, a large population became chronically infected through contaminated blood products prior to the identification of the etiological agent in 1989.[2] HCV is classified in the *Hepacivirus* genus of the Flaviviridae family and, even though six major genotypes have been characterized, genotypes *1a* and *1b* comprise ~70% of documented infections and predominate in the US, Europe, and Japan.[3] As a consequence of a long incubation period of 20–30 years following infection, HCV is now the major cause of liver transplants in the world, and more than 15 000 people die annually in the US alone from developing liver diseases caused by HCV.[4]

The HCV (+)-RNA genome encodes a unique polyprotein of approximately 3000 amino acids, which comprises both structural (core, E1, E2, p7) and nonstructural (NS2–NS5) regions. Following processing by host and viral proteases, NS proteins emerge and harbor enzymatic and other essential functions necessary for viral replication.[5] Several virally encoded enzymatic activities have been targeted for HCV antiviral therapy. Recently, NS3-4A protease inhibitors have received approval for use in combination with the standard of care comprised of the pegylated (PEG) immunomodulatory cytokine interferon-α (IFN-α) and the broad-spectrum antivi-

Received 17 August 2012. Accepted 26 September 2012. Published at www.nrcresearchpress.com/cjc on 17 January 2013.

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This article is part of a Special Issue dedicated to Professor Derrick Clive.

ral agent ribavirin.[6] While these new regimens provide patients with an improved outcome, severe side effects, contraindications, and treatment failures in hard to treat genotype *1* populations are fostering efforts for the search for improved treatment options. Most notably, the search for interferon-free regimens using combinations of direct acting antivirals (DAAs) with improved tolerability and efficacy has become the main focus of current efforts. Indeed, several combinations of DAAs encompassing NS3-4A protease, nucleoside and non-nucleoside NS5B polymerase inhibitors, and NS5A inhibitors have demonstrated the potential for improved outcome in vitro, and more recently in HCV-infected patients.[7]

Our own research efforts in the field have led to the discovery of BILN 2061 (celuprivir), the first NS3-4A protease inhibitor to demonstrate antiviral potency in genotype *1* HCV-infected patients. Faldaprevir, a follow-up analog, is currently in phase 3 clinical trials in combination with PEG-IFN-α2a/ribavirin.[8] A complementary program focusing on the discovery of non-nucleoside inhibitors (NNIs) of the NS5B RNA-dependent RNA polymerase of HCV, led to the development of BILB 1941, an inhibitor of this enzyme that binds to the thumb pocket 1 allosteric site, and was the first "finger loop" inhibitor to provide proof-of-concept for this mechanism in HCV-infected patients.[9] BI 207127 is a more potent follow-up analog of BILB 1941 that is currently in phase 3 clinical trials in an interferon-sparing combination with faldaprevir and ribavirin.[10] As part of our continued efforts toward the development of anti-HCV therapies, we have been involved in a search for structurally and chemically diverse back-up compounds for our lead clinical candidates. Recently, we and others reported the discovery of *N*-acetamide-6-indolecarboxylic acid thumb pocket 1 NS5B inhibitors, which provided an attractive starting point for the development of structure–activity relationship (SAR) distinct from previous series and the discovery of more chemically diverse inhibitors.[11] We report herein the evaluation of acylsulfonamide and acylsulfamide isosteres of these indolecarboxylic acid inhibitors.

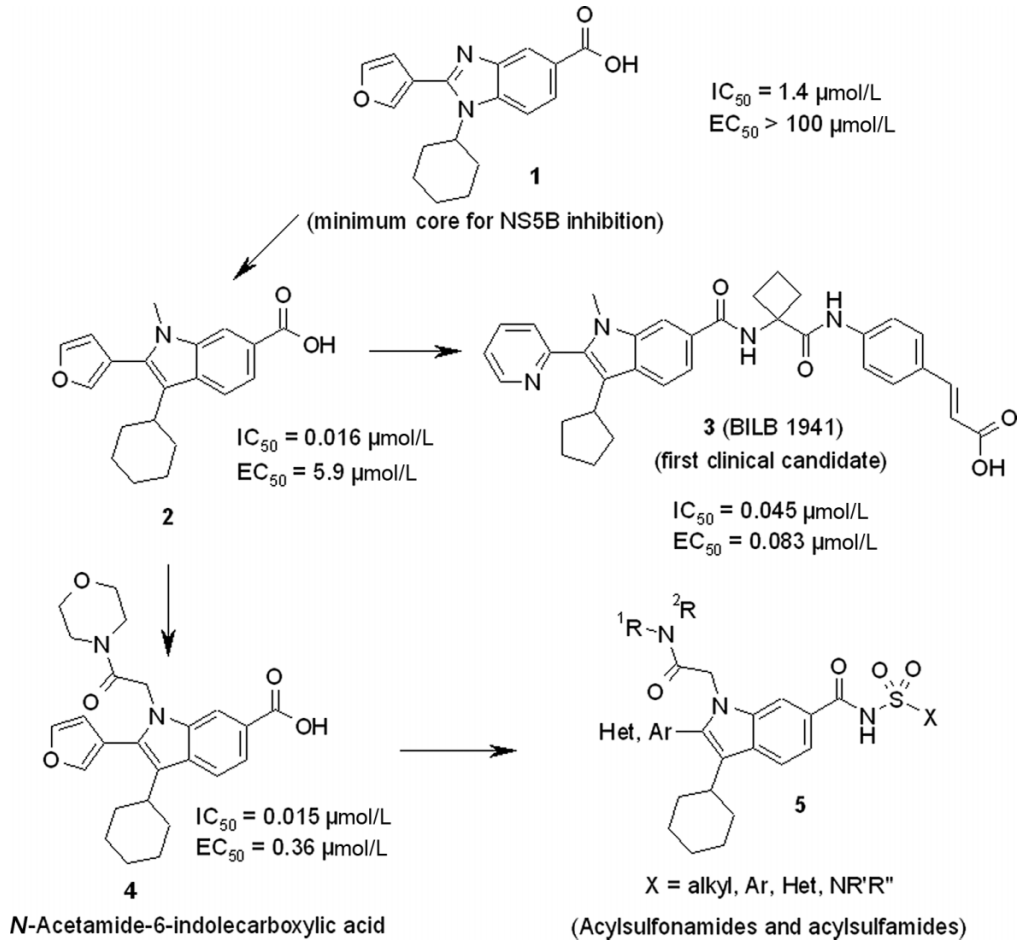
Results and discussion

HCV NS5B is a RNA-dependent RNA polymerase that is virally encoded and is essential for viral replication. It has no mammalian counterpart and thus provides an attractive opportunity for the discovery of specific antiviral agents. The polymerase architecture comprises a thumb, finger, and palm domain, with the latter harboring the enzyme active site.[12] NS5B's key function is to replicate the HCV genome to initiate production of progeny virus. As with other polymerases, it is susceptible to inhibition by nucleoside/nucleotide inhibitors that are anabolized to triphosphate forms and mimic substrate to effect chain termination. In addition, at least four allosteric sites have been described, where NNIs can bind and interfere with enzyme conformational changes that are necessary for RNA synthesis. These include thumb pocket 1 and 2 as well as two distinct sites located in the palm domain of the enzyme, in close proximity to the active site. All classes of HCV NS5B inhibitors (NIs and NNIs) have been validated in clinical trials and have been the subject of several literature reviews.[13] Thumb pocket 1 inhibitors (also referred to as finger loop inhibitors) are believed to function by preventing the closure of a loop that extends from the finger to the thumb domain of the enzyme and the formation of an enclosed active site that can initiate RNA synthesis.[14] Unlike other NS5B allosteric sites, thumb pocket 1 is highly selective in terms of its chemotype preferences and their potential to deliver the potency levels necessary for the development of powerful antiviral agents. Indeed, only benzimidazole derivatives and lipophilic isosteric indole analogs have emerged as attractive starting points for inhibitor design.[15]

Figure 1 provides some historical background on Boehringer Ingelheim's thumb pocket 1 inhibitor program. From screening of our corporate sample collection and preliminary SAR, benzimidazole **1** was quickly identified as the minimum core for polymerase inhibition.[16a] Replacement of the benzimidazole scaffold by an isosteric indole core (compound **2**) resulted in significantly improved intrinsic potency in a biochemical assay using a C-terminally truncated NS5BΔ21 polymerase as previously described (half maximal inhibitory concentration (IC_{50}) = 16 nmol/L).[11a,16b] Cellular permeability was also improved for the lipophilic indoles, resulting in analogs with low micromolar antiviral activity in a cell-based genotype *1b* subgenomic replicon assay (half maximal effective concentration (EC_{50}) = 5.9 μmol/L).[16b] 6-Indolecarboxylic acid (**2**) in turn led to diamide **3** (BILB 1941) with good antiviral activity in vitro (EC_{50} = 84 and 153 nmol/L in genotype *1b* and *1a* replicons, respectively) and proof-of-concept in HCV-infected patients.[9] While efforts were continuing toward further optimization of diamide derivatives such as BILB 1941, a structurally divergent back-up series of inhibitors was discovered by us and others, which took advantage of the availability of the ring nitrogen atom in indole derivatives such as **2** as a new vector for exploring interactions with the protein.[11] *N*-Acetamide indole-6-carboxylic acid derivatives such as **4** provided a chemically diverse starting point with promising cellular potency (EC_{50} = 0.36 μmol/L) for the development of an alternative series. To improve the potency of indole derivatives such as **4** and to address concerns associated with the potential for carboxylic acids to form reactive acylglucuronide metabolites or *S*-acyl-coenzyme A thioesters that could lead to toxicity and idiosyncratic allergic responses in vivo,[11c,17] we explored the potential of acylsulfonamide and acylsulfamide **5** carboxylic acid isosteres as potential NS5B inhibitors.[18] The outcome of this study is reported herein.

Acylsulfonamide and acylsulfamide indole inhibitors were prepared from the corresponding 6-indolecarboxylic acid derivatives through one of the sequences described in Scheme 1. 2-Bromoindole **6**[16b] was alkylated with *tert*-butyl bromoacetate, the *tert*-butyl protecting group cleaved under acidic conditions, and the liberated carboxylic acid coupled to amines under standard amide bond forming protocols to provide intermediates **7**. Introduction of the C-2 aryl or heteroaryl substituent was accomplished under standard metal-catalyzed Suzuki–Miyaura cross-coupling conditions using boronic acid derivatives to provide indole derivatives **8**.[19] Alternatively, **8** could be accessed through a sequence of steps involving initial cross-coupling of 2-bromoindole **6** with boronic acids followed by introduction of the acetamide side chain to provide **9** followed by amide formation.[16b] 3-Cyclohexyl-6-indolecarboxylic acid methyl ester (**10**)[16b] can also serve as starting material to provide intermediate **9** through a sequence involving *N*-acetamide formation, followed by C-2 bromination, Suzuki–Miyaura cross-coupling to introduce the C-2 aryl or heteroaryl substituent,

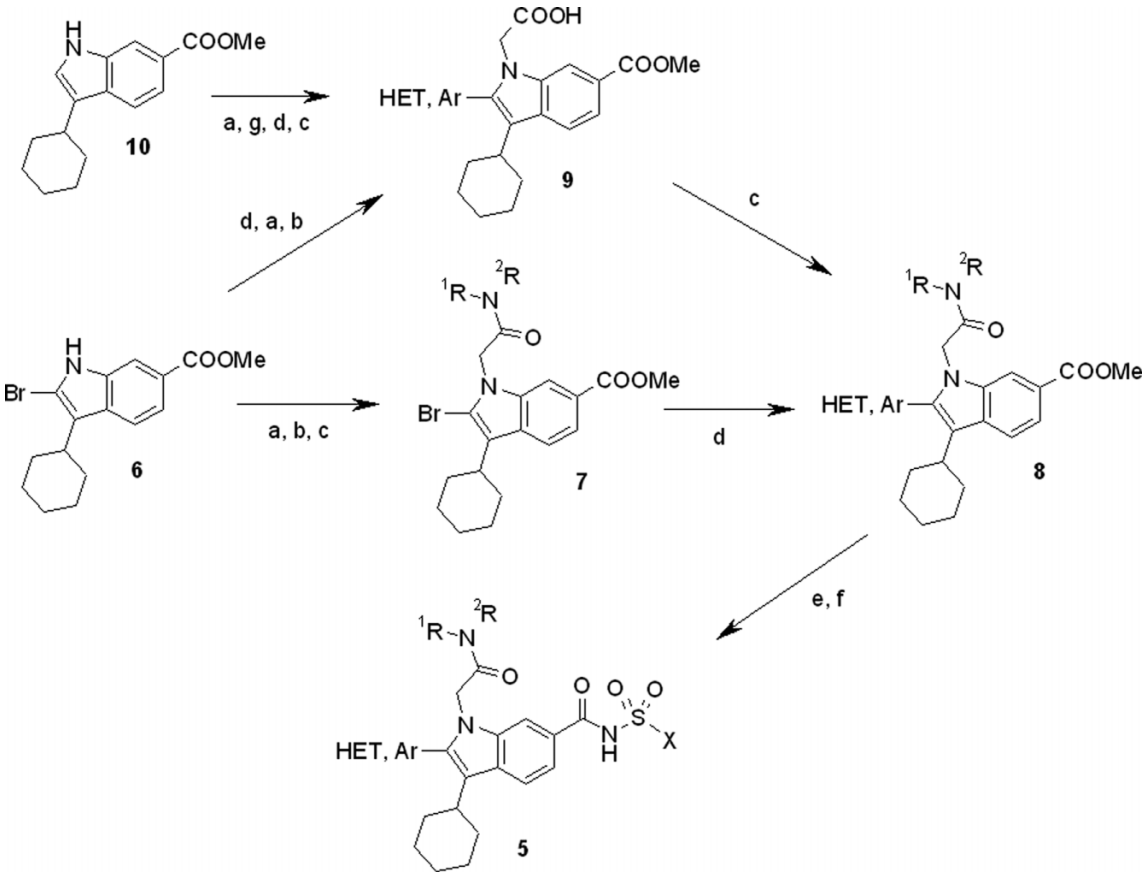
Fig. 1. Evolution of Boehringer Ingelheim's thumb pocket 1 allosteric NS5B inhibitors.



and selective cleavage of the *tert*-butyl ester protecting group. Acylsulfonamides and acylsulfamides **5** were prepared by saponification of ester **8** and coupling of the resulting carboxylic acid with various sulfonamides or sulfamides under standard amide bond forming conditions. An alternative assembly sequence designed for rapid exploration of amide substituents while maintaining the acylsulfonamide moiety constant is described in the Experimental section. It involves the preparation of an indole 6-acylsulfonamide intermediate bearing a free acetic acid side chain on the indole nitrogen and condensation with amines as the last step in the sequence (see the Experimental section for details).

Initial results from the conversion of carboxylic acid **4** to methyl or phenylacylsulfonamide analogs **11** and **12** (Table 1) proved encouraging. Comparable intrinsic potencies in the biochemical enzyme inhibition assay[11a,20] (IC_{50} = 0.015–0.018 μmol/L) were measured for carboxylic acid (**4**) and acylsulfonamide/sulfamide derivatives, suggesting that both functionalities engage in similarly productive interactions with NS5B. In the cell-based replicon assay, however, despite similarities in the calculated pK_a and *A* log *P*[21] values for carboxylic acids and acylsulfonamides, we observed a three- to four-fold reduction in a cell-based antiviral assay (EC_{50} = 0.9–1.5 μmol/L).[22] A comprehensive SAR study was then initiated to identify analogs with improved antiviral potency. Highlights from the evaluation of approximately 40 acylsulfonamide/acylsufamide derivatives are summarized in Table 1. Phenyl acylsulfonamide (**12**) served as a reference point for the investigation of the impact of electronic effects through substitution of the phenyl ring with electron-withdrawing and -donating groups at the ortho-, meta-, and para-positions (results not shown). Despite spanning a calculated pK_a range of 3.7–4.7, there was no significant impact on overall potency. A similar result was obtained with benzylic **13** or lipophilic aromatic systems such as 2-naphthyl **14**. Steric factors on the other hand appeared to be more important with respect to cell-based potency, presumably as a result of shielding the polar and ionized acylsulfonamide moiety. The introduction of a lipophilic *ortho*-methyl group on the phenyl ring (compound **15**) and small sterically encumbering aliphatic groups such as cyclopropyl **16** and *tert*-butyl **17** provided analogs with similar intrinsic potency against the enzyme but submicromolar cell culture potency, possibly because of improved permeation of these analogs through cell membranes. *tert*-Butyl analog **17** had a comparable profile to carboxylic acid **4**. Acylsulfamides (**18**–**21**), which have calculated pK_a values similar to carboxylic acids, were also well tolerated, particularly N,N-disubstituted analogs such as **20** and **21** (EC_{50} < 0.5 μmol/L). Interestingly, *N*-methylation of the acylsulfonamide or replacement of the sulfone moiety by a second carbonyl (imide analog) was not toler-

Scheme 1. Synthesis of inhibitors. Reagents and conditions: (*a*) NaH (1.25 equiv), DMF, 0 °C for 1 h then *tert*-butyl bromoacetate (1.24 equiv), RT, 18 h; (*b*) TFA, 4 h, RT or 4 N HCl in dioxane, RT, 4 h; (*c*) TBTU or HATU (1.2 equiv), Et*i*Pr$_2$N (5 equiv), DMF or DMSO, RT, 10 min then ^{1}R^{2}RNH (1.1 equiv), RT, 1−18 h; (*d*) heteroaryl or aryl boronic acid (1.3 equiv), LiCl (2 equiv), Na_2CO_3 (2.5 equiv), $Pd(PPh_3)_4$ (0.04 equiv), degassed toluene/ethanol/water 1:1:1, reflux overnight under argon; (*e*) 10 N NaOH or LiOH (5−10 equiv), 5:1 THF–water, 1–2 h; (*f*) Oxalyl chloride via acid chloride or, EDAC–HCl, water soluble carbodiimide or carbonyldiimidazole (1.2–2 equiv), DMAP (1.5–2.0 equiv), sulfonamide or sulfamide (1–1.2 equiv), CH_2Cl_2, DMF or DMSO, RT (18−48 h); (*g*) Pyridinium perbromide, THF–$CHCl_3$ (1:1), 0 °C (4 h) then RT overnight. DMF: dimethylformamide, RT: room temperature, TFA: trifluoroacetic acid, TBTU: *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate, HATU: (*O*-(7-azabenzoriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DMSO: dimethyl sulfoxide, THF: tetrahydrofuran, EDAC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP: 4-dimethylaminopyridine.

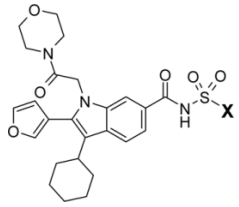


ated. This could be due to the absence of an ionizable group at physiological pH in the latter or an unfavorable conformational change (results not shown).

The lack of distinctive electronic or steric SAR trends that emerged from modification of the sulfonamide/sulfamide moiety suggested that this part of the bound inhibitor was likely solvent-exposed. This was confirmed when compound **12** was soaked into NS5BΔ21 crystals and an X-ray crystal structure of the complex was solved. The crystal packing of this complex includes two protein molecules per asymmetric unit (referred to as A and B). The inhibitor was visible on molecule B and not observed on molecule A. Inhibitor **12** bound the thumb pocket 1 allosteric site as previously reported for analogous indole-6-carboxylic acids.[14a,23] Upon binding of compound **12** to molecule B, electron density corresponding to NS5B residues 18–35 (the Λ1 finger loop) was apparently displaced and not seen (Fig. 2A). In the apo structure, this pocket is not solvent accessible and is sequestered by the residues from the Λ1 finger loop. Figure 2B depicts the overlap between the Λ1 finger loop and inhibitor **12** binding sites. In contrast, the finger loop of molecule A was blocked by a crystal contact and cannot open to reveal the allosteric binding site, and thus remains in an apo conformation (without inhibitor).

As depicted in Fig. 3A, the hydrophobic protein interactions made by this class of inhibitor are similar in nature to those mediated by finger loop residues Ser29, Leu30, and Leu31. The cyclohexyl ring of **12** occupies the majority of a well-defined hydrophobic pocket (Leu30 subpocket), the indole scaffold stacks against proline residues (P495), and the furan ring lies in a somewhat less-defined hydrophobic area (Leu31 subpocket). A key anchoring point that is critical for inhibitor potency is provided by a strong hydrogen bond between the carbonyl moiety of the acylsulfonamide functionality and the guanidine side chain of Arg503 (Fig. 3A). Similarly, a salt bridge was observed between the carboxylic acid moiety of previously reported indole-6-carboxylic acid analogs and the guanidine group of Arg503.[14a,23] Analogs containing a "reverse" acylsulfonamide in which the SO_2 moiety is attached to the indole ring were previously explored in a less active benzimidazole-based series of inhibitors. In this disposition,

Table 1. Hepatitis C virus (HCV) NS5BΔ21 enzyme inhibition and antiviral potency data for acylsulfonamide and acylsulfamide derivatives.



Compound	X	IC_{50} (μmol/L)[a]	EC_{50} (μmol/L)[a]	*A* log *P*[b]
11	CH_3	0.015	1.5	3.27
12	Ph	0.018	0.94	4.85
13	Bn	0.059	0.94	4.86
14	2-Naphthyl	0.038	1.05	5.76
15		0.028	0.67	5.37
16		0.017	0.69	3.76
17		0.047	0.37	4.21
18	NHPh	0.058	2.1	4.24
19	NHMe	0.045	1.53	2.66
20	NMe_2	0.017	0.34	2.87
21		0.049	0.46	3.33

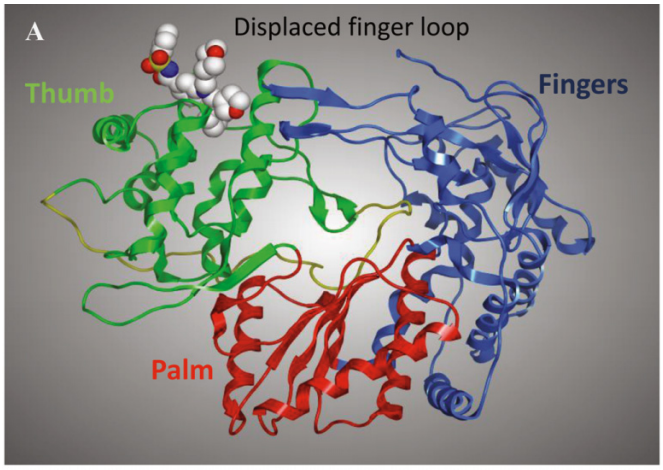
[a]Values are an average of at least two measurements.
[b]See ref. 21.

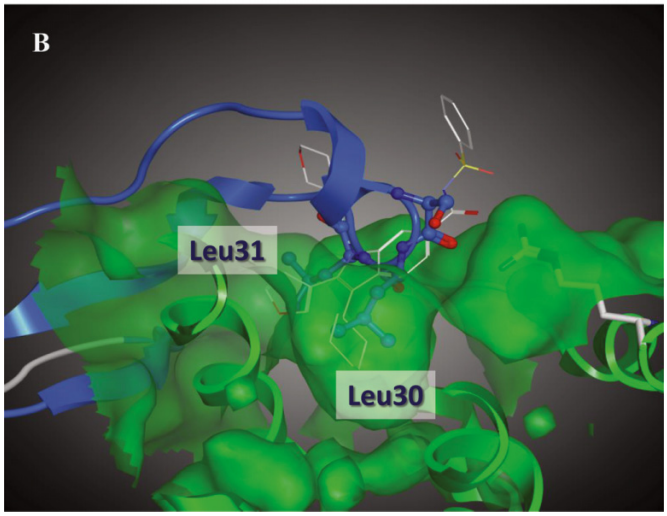
hydrogen bonding to Arg503 may be less favorable and the compounds were found to be inactive. Therefore, these were not investigated in the current indole chemotype (unpublished data). The acylsulfonamide/sulfamide moiety is a good replacement of the carboxylate group as a strong hydrogen bond with Arg503 is maintained. Furthermore, one of the sulfone oxygen atoms makes an additional weak interaction (2.7 Å) with the same guanidine side chain of Arg503. In this bound conformation, the phenyl group is pointing toward solvent, orthogonal to the protein surface. This is in agreement with the SAR described in Table 1 and the fact that methyl analog **11** or bulkier substituents (e.g., 2-napthyl group of **14**) could be accommodated with potencies comparable to **12**.

Figure 3B depicts the overlay of acylsulfonamide **12** and an analogous indole-6-carboxylic inhibitor.[23] The two molecules bound similarly to NS5B, and minimal protein movement is required to accommodate the two classes of inhibitors. The acylsulfonamide moiety induced a small torsion (~8°) of the carbonyl out of plane with the indole core bringing it toward Arg503. A good correspondence was observed for the indole scaffolds, however, the lipophilic cyclohexyl ring of **12** appears to insert slightly deeper into its lipophilic pocket (average shift of ~0.5 Å). Both acetamide substituents project into the solvent, explaining the lack of improvement in intrinsic potency through modification of these two susbstituents.

Having identified analogs with overall potency profiles comparable to the starting 6-indole carboxylic acid **4** and being less likely to generate reactive metabolites (e.g., acyl-

Fig. 2. Panel A shows inhibitor **12** bound to NS5BΔ21 thumb pocket 1 with the displaced Λ1 finger loop. The thumb domain is depicted in green and the palm and finger domains are red and blue, respectively. Panel B depicts an overlay of apo NS5B with the Λ1 finger loop in the closed conformation and inhibitor **12** bound in thumb pocket 1. The inhibitor **12** (in white) and Λ1 finger loop residues Ser29, Leu30, and Leu31 (ball and stick) occupy the same region in the thumb domain.

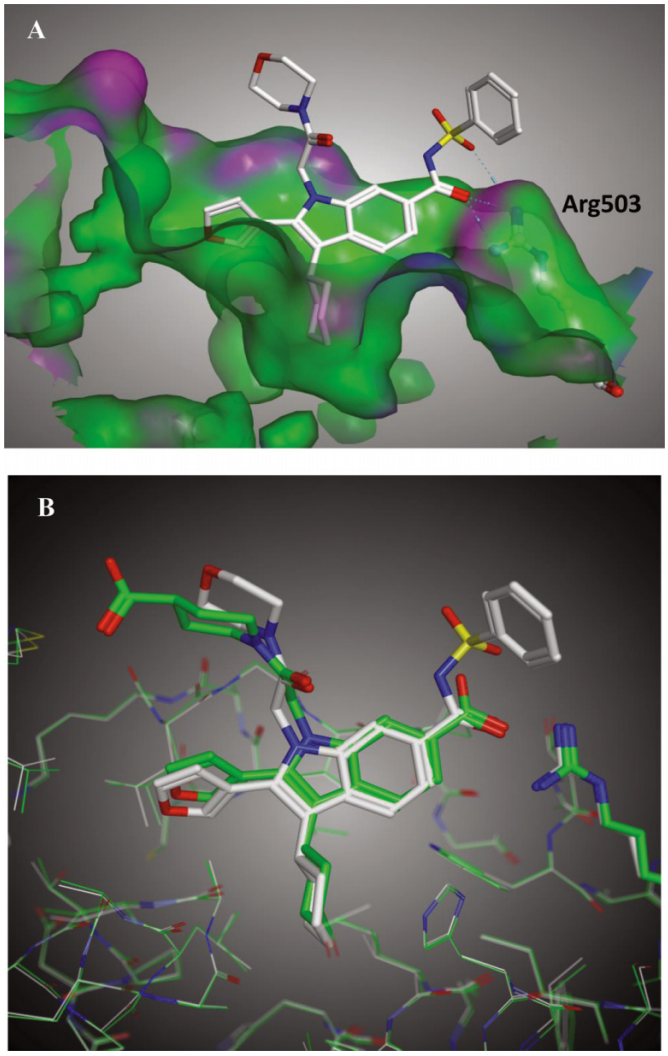




glucuronides), we next investigated the impact of modifying the indole acetamide substituent in *tert*-butyl acylsulfonamide derivatives. Consistent with this portion of the inhibitor being exposed to solvent (vide supra), results depicted in Table 2 revealed a rather flat SAR, with most analogs maintaining intrinsic as well as antiviral potency in a similar range. Interestingly, analogs with a basic amide side chain and expected to exist as zwitterionic species (e.g., piperazine **25** and 4-aminopiperidine **28**) provided the best cellular activities, despite an increase in polarity (*A* log *P* ~ 3) associated with the strongly ionized state of these molecules. Similar observations were made in the carboxylic acid series where zwitterionic derivatives displayed improved cell culture activity.[11]

Although the best analogs at this stage of our investigations addressed the potential metabolic liability associated with the carboxylic acid derivatives, they still required a significant im-

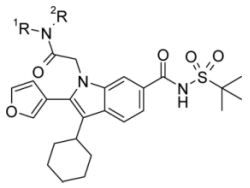
Fig. 3. Panel A shows inhibitor **12** bound to thumb pocket 1 of HCV NS5BΔ21 with key hydrogen bonds between the acylsulfonamide moiety and the guanidine side chain of Arg503. Panel B provides an overlay of an indole-6-carboxylic acid inhibitor and compound **12**.[23]

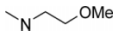
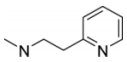
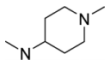


provement in antiviral potency (>10-fold) to compare favorably with our first clinical candidate BILB 1941. In addition, the furyl substituent at the C-2 position of the indole scaffold represented a potential toxicophore that required replacement.[24] Exploiting ongoing SAR studies that were conducted in parallel in the carboxylic acid series by us (data to be published separately) and others,[11] we prepared a matrix of compounds featuring more optimal C-2 substituents and basic acetamide side chains in combination with our best acylsulfonamide (cyclopropyl) and acylsulfamide (*N*,*N*-dimethylsulfamide). Biological results are presented in Table 3.

As anticipated from studies performed in the carboxylic acid series (unpublished data), the building blocks used for this matrix led to inhibitors that were active in biological assays. All compounds inhibited NS5B enzymatic activity with IC_{50} < 100 nmol/L and several achieved antiviral potency <20 nmol/L in the cell-based subgenomic *1b* replicon (**32**, **41**, **43**, **44**, **45**, and **47**) representing a four- to eight-fold

Table 2. Hepatitis C virus (HCV) NS5BΔ21 enzyme inhibition and antiviral potency data for a series of acyl *tert*-butylsulfonamide acetamide analogues.



Compound	$^1R_N{}^2R$	IC_{50} (μmol/L)[a]	EC_{50} (μmol/L)[a]	*A* log *P*[b]
17		0.047	0.37	4.21
22		0.058	0.78	4.52
23		0.10	0.48	5.43
24		0.073	0.96	4.98
25		0.12	0.31	2.91
26		0.028	0.67	4.39
27		0.21	0.93	5.40
28		0.047	0.37	3.07

[a]Values are an average of at least two measurements.
[b]See ref. 21.

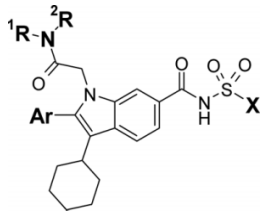
improvement over clinical candidate BILB 1941. Genotype *1a* HCV is a predominant subtype in the USA and constitutes a hard to treat patient population for which IFN-based treatments are often less effective. Representative compounds (**29**, **31**, and **33**) were tested in a genotype *1a* subgenomic replicon[25] and a greater than twofold upward shift in antiviral potency was observed (EC_{50} = 95, 81, and 42 nmol/L, respectively).

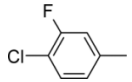
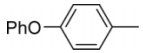
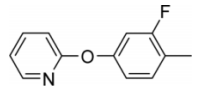
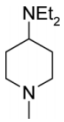
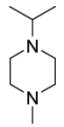
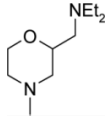
Having identified analogs with improved potency over clinical candidate BILB 1941 and with lower potential to form reactive metabolites compared with indole-6-carboxylic acid derivatives such a **4**, we evaluated the in vitro absorption, distribution, metabolism, and excretion (ADME) properties of representatives of this class of compounds prior to assessing oral bioavailability in rats. As seen in Table 4, potent zwitterionic inhibitors displayed low aqueous solubility at pH 6.8. Although these compounds generally showed good metabolic stability following incubation with human or rat liver microsomes ($T_{1/2}$ > 100 min), they had poor apical to basolateral permeability in the Caco-2 model of oral absorption. Consequently, none of the compounds tested in vivo showed plasma exposure following oral administration to rats. Compounds **40** and **41** were the only two analogs with measurable quantities of inhibitor detected in the target liver organ, corresponding to approximately 20-fold in the EC_{50}.

Conclusion

In summary, we have evaluated acylsulfonamides and acylsulfamides as isosteric replacements for the carboxyl function

Table 3. Hepatitis C virus (HCV) NS5BΔ21 enzyme inhibition and antiviral potency data for a matrix of acylsulfonamide and acylsulfamide analogues.



												
	Compound	X	IC_{50} (μmol/L)[a]	EC_{50} (μmol/L)[a]	Compound	X	IC_{50} (μmol/L)[a]	EC_{50} (μmol/L)[a]	Compound	X	IC_{50} (μmol/L)[a]	EC_{50} (μmol/L)[a]
					**29**	*t*-Bu	0.042	0.078				
	30	Cyclo-Pr	0.069	0.083	**32**	Cyclo-Pr	0.052	0.017	**34**	Cyclo-Pr	0.050	0.075
	31	NMe_2	0.081	0.055	**33**	NMe_2	0.062	0.027	**35**	NMe_2	0.039	0.026
	**36**	Cyclo-Pr	0.095	0.088	**38**	Cyclo-Pr	0.080	0.034	**40**	Cyclo-Pr	0.043	0.023
	37	NMe_2	0.092	0.28	**39**	NMe_2	0.090	0.023	**41**	NMe_2	0.044	0.016
	**42**	Cyclo-Pr	0.065	0.050	**44**	Cyclo-Pr	0.066	0.016	**46**	Cyclo-Pr	0.052	0.031
	43	NMe_2	0.071	0.013	**45**	NMe_2	0.051	0.013	**47**	NMe_2	0.047	0.011

[a]Values are an average of at least two measurements.

Table 4. In vitro and in vivo absorption, distribution, metabolism, and excretion (ADME)-PK (pharmacokinetic) profiles of representative acylsulfonamide and acylsulfamide NS5B inhibitors.

Compound	Solubility pH 6.8/2 (μg/mL)[a]	HLM/RLM $T_{1/2}$ (min)[a]	Caco-2 ($\times 10^{-6}$ cm/s)[b]	$C_{1h/2h}$ (μmol/L)[c]	$[Liver]_{2h}$ (μmol/L)[d]
29		>300/>300	<0.1	BLD	BLD
33	0.3/4.0	>300/>300	<0.1	BLD	BLD
40	10/544	190/101	0.22	BLD	0.41
41	4.9/12	141/161	1.4	BLD	0.49
43	4.6/15	288/>300	<0.1	BLD	BLD

HLM, human liver microsomes; RLM, rat liver microsomes; BLD, below limit of detection.
[a]Measured on lyophilized amorphous solids using the 24 h shaking flask method and pH 7.2 phosphate buffer.
[b]The Caco-2 permeability assays were run without bovine serum albumin (BSA) with both chambers at pH 7.4.
[c]Plasma concentration at 1 and 2 h following oral administration to rats as mixtures of four compounds at a dose of 4 mg/kg each.
[d]Liver concentrations were measured as described in the Experimental section.

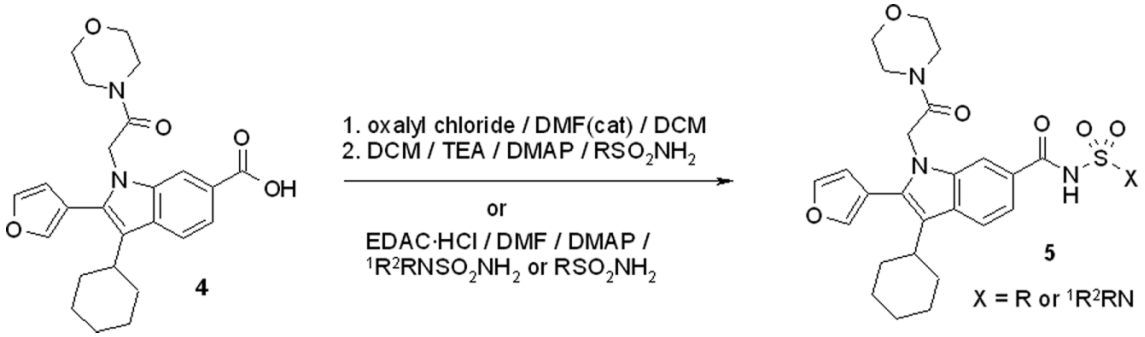
of previously described *N*-acetamide-indole-6-carboxylic acid inhibitors of HCV NS5B polymerase that bind in the thumb pocket 1 allosteric site. The new analogues showed improved antiviral potency in genotype *1a* and *1b* replicons compared with the previous clinical candidate, BILB 1941. The binding-site and protein-inhibitor interactions of an acylsulfonamide analog were characterized by X-ray crystallography and are consistent with the reported SAR. However, significant improvements in permeability and oral absorption are required prior to further advancement of this chemical series.

Experimental

Instrumentation, analysis, and starting materials

All commercially obtained solvents and reagents were used as received without further purification. 6-Indolecarboxylic acid esters **6** and **10** were prepared as previously described.[16b] Phenylsulfamide was prepared as previously described.[26] All reactions were carried out under an atmosphere of argon. Temperatures are given in degrees Celsius. Solution percentages express a weight-to-volume relationship and solution ratios express a volume-to-volume relationship, unless stated otherwise. NMR spectra were recorded on a Bruker AVANCE II (400 MHz for ^{1}H NMR) spectrometer and were referenced to either DMSO-d_6; (2.50 ppm) or $CDCl_3$ (7.27 ppm). Data is reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, br = broad, and m = multiplet), integration, and coupling constant (*J*; reported to the nearest 0.5 Hz). Low-resolution mass spectra were obtained on a Micromass Platform LCZ model ZMD 4000 in electrospray mode. High-resolution mass spectra (HR-MS) were obtained on a Bruker micrOTOF-Q II in electrospray positive (ES^+) ionization mode. Purification of crude material was performed either by flash column chromatography or by using a CombiFlash Companion using RediSep Silica or SilicaSep columns according to preprogrammed gradient and flow rate separation conditions in hexane/EtOAc or dichloromethane (DCM)/MeOH. The final compounds were purified by preparative HPLC on a Waters 2767 Sample Manager with pumps 2525, column fluidics organizer (CFO), photodiode array (PDA) detector 2996, and MassLynx 4.1 using either a Whatman Partisil 10-ODS-3 column, 2.2 cm × 50 cm or a YMC Combi-Prep ODS-AQ column, 50 mm × 20 mm inside diameter (ID), S-5 μm, 120 Å, and a linear gradient program from 2% to 100% AcCN/water (0.06% trifluoroacetic acid (TFA)). Fractions were analyzed by analytical HPLC, and the pure fractions were combined, concentrated, frozen, and lyophilized to yield the desired compound as a neutral entity or the trifluoroacetate salt for basic analogues. Inhibitor HPLC purity was measured by using a Waters Alliance 2695 separation module with a Waters TUV 2487 UV detector. The column was a Combiscreen ODS-AQ, 5 μm, 4.6 mm × 50 mm, linear gradient from 5% to 100% ACN/H2O + 0.06% TFA in 10.5 min with detection at 220 nm.

General procedure for preparing compounds 11–21



Acid chloride method

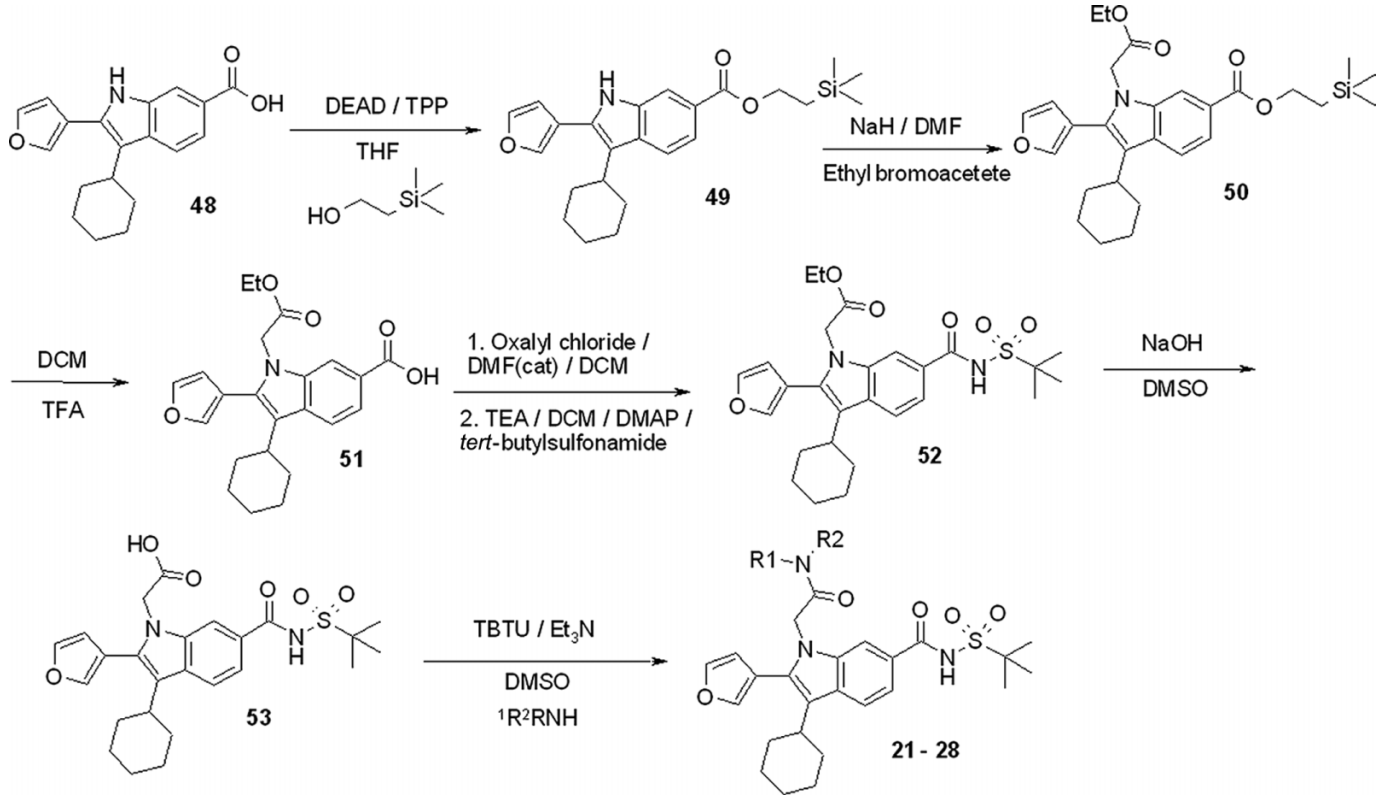
To a solution of compound **4**[11a] (50.3 mg, 0.16 mmol) in DCM (1.5 mL) at room temperature (RT) was added a 2.0 mol/L solution of oxalyl chloride in DCM (144 μL, 0.29 mmol) and dimethylformamide (DMF; 10 μL). After 20 min, volatiles were removed under reduced pressure. The crude acid chloride intermediate was redissolved in DCM (1.5 mL) and *tert*-butyl sulfonamide (23.6 mg, 0.17 mmol), 4-dimethylaminopyridine (DMAP; 14.0 mg, 0.12 mmol), and triethylamine (TEA; 48 μL, 0.35 mmol) were added successively and the resultant mixture stirred for 30 min. After evaporation of volatiles, the residue was dissolved in DMSO (1.5 mL) and the mixture acidified with TFA (44 μL). The desired material was isolated and purified using reversed-phase preparative (RP-prep) HPLC using an acetonitrile (ACN)/water gradient incorporating 0.1% TFA as buffer. Following collection, pooling, and lyophilization of relevant fractions, compound **17** was obtained (33 mg, 51% yield) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.30 (s, 1H), 8.00 (d, 1H, J = 1.1 Hz), 7.90 (t, 1H, J = 1.7 Hz), 7.86–7.80 (m, 2H), 7.59 (dd, 1H, J = 1.4, 8.5 Hz), 6.53 (d, 1H, J = 1.1 Hz), 5.02 (s, 2H), 3.61–3.51 (m, 8H), 2.76–2.65 (m, 1H), 2.00–1.64 (m, 7H), 1.43 (s, 9H), 1.37–1.22 (m, 3H). HR-MS (positive atmospheric pressure photoionization (APPI$^+$)) calcd for $C_{29}H_{37}N_3O_6SH$ [M + H]$^+$: 556.2476; found: 556.2477.

Compounds **13**–**15** were prepared in a similar fashion.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDAC)–HCl method

To a solution of carboxylic acid **4**[11a] (20.0 mg, 0.046 mmol) in DMF (1.0 mL) was added DMAP (11 mg, 0.09 mmol), *N,N*-dimethylsulfamide (6.9 mg, 0.056 mmol), and EDAC–HCl (17.6 mg, 0.092 mmol), and the mixture stirred for 2 d at RT. The desired material was isolated and purified using RP-prep HPLC using an ACN/water gradient incorporating 0.1% TFA as buffer. Following collection, pooling, and lyophilization of relevant fractions, compound **20** was isolated (13 mg, 52% yield) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.58 (s, 1H), 8.07 (d, 1H J = 1.2 Hz), 7.92 (t, 1H, J = 1.6 Hz), 7.85 (s, 1H), 7.83 (m, 1H), 7.64 (dd, 1H, J = 1.6, 8.2 Hz), 6.53 (dd, 1H, J = 0.8, 1.6 Hz), 5.30–5.11 (m, 1H), 5.03 (s, 2H), 3.6–3.4 (m, 8H), 2.92 (s, 6H), 2.75–2.65 (m, 1H), 2.04–1.59 (m, 7H), 1.32 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.3, 166.1, 144.1, 142.5, 136.7, 131.9, 129.3, 123.7, 119.5, 119.4, 118.6, 115.1, 111.9, 111.2, 66.2, 44.8, 42.1, 38.0, 36.3, 32.8, 26.6, 25.6. HR-MS (APPI$^+$) calcd for $C_{27}H_{34}N_4O_6SH$ [M + H]$^+$: 543.2272; found: 543.2275.

Compounds **11**, **12**, **16**, **18**, **19**, and **21** were prepared in a similar fashion.



General procedure for compounds 22–28

Intermediate 49

To a solution of compound **48**[11a] (1.08 g, 3.5 mmol) in tetrahydrofuran (THF; 20 mL) was added 2-(trimethylsilyl)ethanol (751 μL, 5.2 mmol) and diethyl azodicarboxylate (DEAD; 825 μL, 5.2 mmol). Triphenylphosphine (1.37 g, 5.2 mmol) was added and the mixture stirred overnight. Volatiles were removed under reduced pressure and the desired material purified on silica gel using a 5%–20% ethyl acetate/hexane gradient to obtain compound **49** as an off-white solid (520 mg, 38% yield; 97% homogeneity). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.38 (s, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.87 (s, 1H), 7.80 (d, 1H, J = 8.6 Hz), 7.56 (dd, 1H, J = 1.4, 8.6 Hz), 6.85 (d, 1H, J = 1.4 Hz), 4.38 (t, 2H, J = 8.0 Hz), 2.92 (m, 1H), 2.02–1.70 (m, 7H), 1.47–1.34 (m, 3H), 1.10 (t, 2H, J = 8.0 Hz), 0.10 (s, 9H).

Intermediate 50

To a solution of intermediate **49** (939 mg, 2.29 mmol) in DMF (10 mL) under nitrogen was added sodium hydride (60% in mineral oil, 96 mg, 2.4 mmol) in one portion and the solution was stirred until hydrogen evolution had ceased (about 15 min). To the dark yellow solution was added ethyl bromoacetate (381 μL, 3.44 mmol) and the mixture stirred for a further 60 min. The reaction was diluted with ethyl acetate and washed successively with saturated NH_4Cl, water, and brine, dried over $MgSO_4$, filtered through a plug of silica, and evaporated. The desired material, purified on silica gel using a 5%–20% ethyl acetate/hexane gradient, was obtained as a light yellow gum (877 mg, 77% yield; 98% homogeneity). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.04 (s, 1H), 7.90 (d, 1H, J = 1.4 Hz), 7.88–7.83 (m, 2H), 7.66 (dd, 1H, J = 1.1, 8.5 Hz), 6.55 (d, 1H, J = 0.8 Hz), 4.96 (s, 2H), 4.39 (t, 2H, J = 8.0 Hz), 4.09 (q, 2H, J = 7.0 Hz), 2.73–2.64 (m, 1H), 1.94–1.66 (m, 7H), 1.45–1.20 (m, 3H), 1.20–1.03 (m, 6H), 0.07 (s, 9H).

Intermediate 51

Trifluoroacetic acid (2.0 mL) was added to a solution of compound **50** (850 mg, 1.72 mmol) in DCM (10.0 mL) and this was stirred at RT overnight. Volatiles were evaporated under reduced pressure. Solid residues were suspended in diethyl ether and stirred briefly. Solids were filtered, washed with more diethyl ether, then air-dried. Intermediate **51** (464 mg, 68% yield; 99% homogeneity) was obtained as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.60 (s, 1H), 8.04 (s, 1H), 7.89 (d, 1H, J = 1.6 Hz), 7.86 (s, 1H), 7.82 (d, 1H, J = 8.4 Hz), 7.65 (dd, 1H, J = 1.1, 8.3 Hz), 6.55 (d, 1H, J = 1.0 Hz), 4.96 (s, 2H), 4.09 (q, 2H, J = 7.2 Hz), 2.68 (m, 1H), 1.94–1.64 (m, 7H), 1.40–1.22 (m, 3H), 1.14 (t, 3H, J = 7.2 Hz). Flow-injection analysis (FIA)-MS (APPI$^+$) m/z: 396.2 [M + H]$^+$.

Intermediate 52

To a solution of compound **51** (448 mg, 1.13 mmol) in DCM (10 mL) at RT was added a 2.0 mol/L solution of oxalyl chloride in DCM (1.13 mL, 2.27 mmol) and DMF (10 μL). After 1 h, volatiles were removed under reduced pressure. The crude acid chloride intermediate was redissolved in DCM (10 mL) and *tert*-butyl sulfonamide (233 mg, 1.70 mmol), DMAP (138 mg, 1.13 mmol), and TEA (474 μL, 3.40 mmol) were added. The resultant mixture was stirred for 2 h and then diluted with ethyl acetate. The solution was washed successively with saturated 1 mol/L $KHSO_4$ and brine, dried over $MgSO_4$ filtered, and volatiles evaporated under reduced pressure. Solid residues were suspended in a mixture of diethyl ether and hexane and stirred briefly. Solids were filtered, washed with more diethyl ether/hexane mixture, then air-dried. Compound **52** (520 mg, 89% yield; 96% homogeneity) was obtained as a pale yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.27 (s, 1H), 8.16 (s, 1H), 7.95 (s, 1H), 7.90 (s, 1H), 7.85 (d, 1H, J = 8.6 Hz), 7.62 (d, 1H, J = 8.4 Hz), 6.57 (s, 1H), 4.96 (s, 2H), 4.10 (q, 2H, J = 7.0 Hz), 2.68 (m, 1H), 1.94–1.63 (m, 7H), 1.42 (s, 9H), 1.36–1.21 (m, 3H), 1.14 (t, 3H, J = 7.0 Hz). FIA-MS (APPI$^+$) m/z: 515.0 [M + H]$^+$.

Intermediate 53

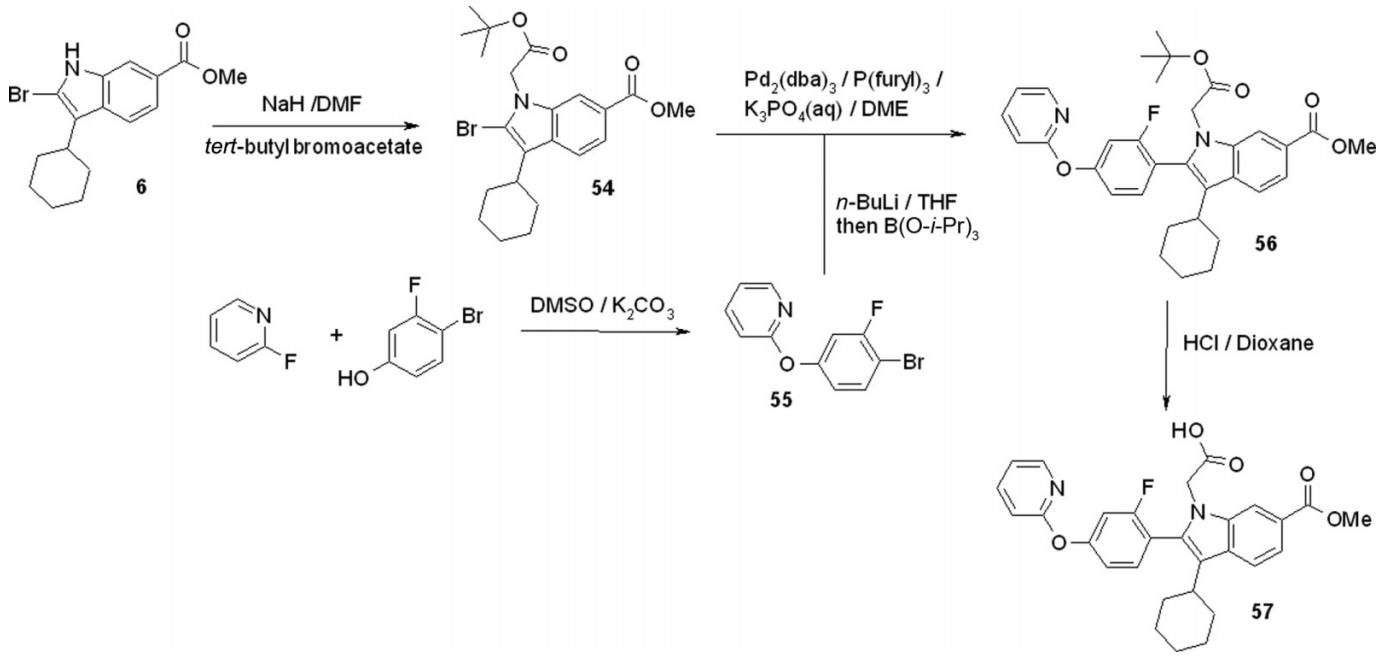
To a solution of compound **52** (500 mg, 0.97 mmol) in DMSO (7 mL) at RT was added 10 mol/L aqueous NaOH (390 μL, 3.88 mmol) and this was stirred for 30 min. The mixture was diluted with ethyl acetate and washed successively with saturated 1 mol/L $KHSO_4$ and brine, dried over $MgSO_4$ filtered, and volatiles evaporated under reduced pressure. The solid residues were suspended in diethyl ether and stirred briefly. Solids were filtered, washed with more diethyl ether, then air-dried to give compound **53** (404 mg, 86% yield; 99% homogeneity) as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.09 (br s, 1H), 11.29 (br s, 1H), 8.16 (s, 1H), 7.92–7.86 (m, 2H), 7.84 (d, 1H, J = 8.6 Hz), 7.62 (d, 1H, J = 8.6 Hz), 6.57 (s, 1H), 4.84 (s, 2H), 2.68 (m, 1H), 1.96–1.64 (m, 7H), 1.43 (s, 9H), 1.37–1.23 (m, 3H). FIA-MS (APPI$^+$) m/z: 487.2 [M + H]$^+$.

Compound 26

To a solution of intermediate **53** (15 mg, 0.031 mmol) in DMSO (1.0 mL) were added *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU; 12 mg, 0.037 mmol), TEA (13 μL, 0.093 mmol), and *N*-(2-methoxyethyl)methyl amine (5 μL, 0.047 mmol). This mixture was stirred overnight at RT, following which TFA (12 μL) was added to acidify. The desired material was isolated and purified using RP-prep HPLC using an ACN/water gradient incorporating 0.1% TFA as buffer. Following collection, pooling, and lyophilization of relevant fractions, compound **26** was obtained (14 mg, 82% yield) as a white amorphous solid. ^{1}H NMR (mixture of rotamers; 400 MHz, DMSO-d_6) δ: 11.40–11.25 (two s, 1H), 8.01–7.73 (m, 4H), 7.58 (dd, 1H, J = 1.4, 8.4 Hz), 6.54–6.48 (m, 1H), 5.07–4.94 (two s, 2H), 3.60–3.35 (m, 4H), 3.33–2.81 (four s, 6H), 2.78–2.66 (m, 1H), 1.99–1.66 (m, 7H), 1.44 (s, 9H), 1.33 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.7, 167.3, 166.2, 166.0, 144.0, 143.9, 142.2, 136.6, 132.2, 131.9, 129.3, 129.2, 124.7, 124.6, 119.5, 119.4, 119.3, 119.2, 119.1, 118.6, 115.2, 115.1, 112.0, 111.8, 111.2, 69.3, 69.2, 61.3, 58.5, 58.0, 48.0, 46.9, 45.2, 36.3, 34.9, 33.2, 32.7, 26.6, 25.6, 24.2. HR-MS (APPI$^+$) calcd for $C_{29}H_{39}N_3O_6SH$ [M + H]$^+$: 558.2632; found: 558.2633.

Compounds **22**–**25** and **27**–**28** were prepared in a similar fashion.

General procedure for the preparation of compounds 34, 35, 40, 41, 46, and 47



Intermediate 54

To a solution of compound **6**[16b] (50.9 g, 151 mmol) in DMF (300 mL) under nitrogen and cooled to 0 °C was added sodium hydride (60% in mineral oil, 9.09 g, 227 mmol) in one portion. This was stirred for 30 min then *tert*-butyl bromoacetate (33.5 mL, 227 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for a further 3 h. After quenching with acetic acid, the product was partitioned between EtOAc and water. The organic portion was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Compound **54** was purified by repeated trituration with dichloromethane/hexane mixtures to afford a yellow solid (55.5 g, 82% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.15 (d, 1H, J = 1.2 Hz), 7.84 (d, 1H, J = 8.6 Hz), 7.68 (dd, 1H, J = 1.2, 8.6 Hz), 5.11 (s, 2H), 3.88 (s, 3H), 2.94–2.79 (m, 1H), 2.02–1.81 (m, 4H), 1.80–1.64 (m, 3H), 1.48–1.33 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.2, 166.9, 136.3, 129.0, 122.6, 120.0, 119.9, 118.9, 116.0, 111.9, 81.8, 51.9, 46.9, 37.1, 31.7, 27.6, 26.5, 25.5. HR-MS (APPI$^+$) calcd for $C_{22}H_{28}BrNO_4Na$ [M + Na]$^+$: 472.1094; found: 472.1084.

Intermediate 55

4-Bromo-3-fluorophenol (25.0 g, 131 mmol) was dissolved in DMSO (330 mL). 2-Fluoropyridine (14.3 mL, 196 mmol) was added, followed by potassium carbonate (45.3 g, 328 mmol). The reaction mixture was heated to 120 °C and stirred at this temperature for 30 h. After cooling to room temperature, water was added and the compound extracted with EtOAc. The organic portion was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification on silica gel and elution with 10:1 hexane/EtOAc provided compound **55** as a light-yellow oil (24.6 g, 70% yield; 95% homogeneity) that was used directly in the next step.

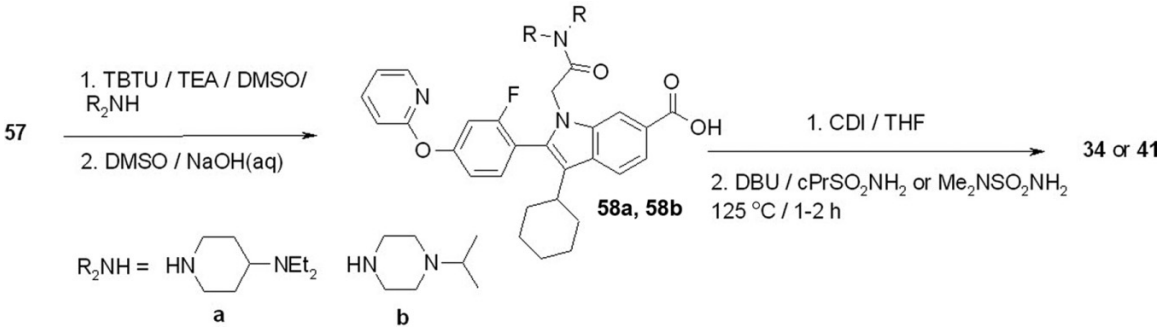
Intermediate 56

Compound **55** from the previous step (15.7 g, 58.7 mmol) was dissolved in THF (150 mL) and cooled to –78 °C. *n*-Butyl lithium (2.3 mol/L in hexanes, 26.8 mL, 61.6 mmol) was added dropwise. Following this addition, the reaction was stirred for 40 min and then triisopropylborate (27.0 mL, 117 mmol) was added dropwise. This mixture was stirred for 30 min at –78 °C, then warmed to room temperature over a period of 3 h. Compound **54** was added as a solid to the reaction mixture (13.2 g, 29.3 mmol) followed by $Pd_2(dba)_3$ (537 mg, 0.587 mmol) and P(2-furyl)$_3$ (817 mg, 3.52 mmol). Solid potassium phosphate (31.1 g, 146 mmol) was dissolved in predegassed water (150 mL) and was added, followed by dimethoxyethane (DME; 300 mL). The mixture was warmed to reflux and stirred for 10–12 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The product was extracted with EtOAc. The combined organic portions were washed with brine and dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification on silica gel, eluting with 5:1 hexane/EtOAc, afforded compound **56** as a light-yellow solid (7.64 g) that was used for the next step.

Intermediate 57

Ester **56** (7.64 g, 13.7 mmol) from the previous step was added to 4 mol/L HCl/1,4-dioxane (120 mL) and the mixture was stirred for 3 h at room temperature. The resulting heterogeneous mixture was filtered and the solids washed with dichloromethane and dried under high vacuum. This material was resuspended in 10:1 dichloromethane/methanol, sonicated for 30 min, and then filtered, washed with dichloromethane, and dried. This procedure was repeated once more to provide compound **57** as an off-white solid (3.87 g, 26% overall yield from bromoindole **54**). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.32–8.27 (m, 1H), 8.10 (d, 1H, J = 1.2 Hz), 8.00–7.93 (m, 1H), 7.90 (d, 1H, J = 8.6 Hz), 7.71 (dd, 1H, J = 1.4, 8.4 Hz),

7.38 (t, 1H, J = 8.6 Hz), 7.32 (dd, 1H, J = 2.3, 10.6 Hz), 7.29–7.24 (m, 1H), 7.22–7.13 (m, 2H), 4.93 (d, 1H, J = 18.0 Hz), 4.68 (d, 1H, J = 18.0 Hz), 3.87 (s, 3H), 2.50 (m, 1H), 1.92–1.61 (m, 7H), 1.39–1.17 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8, 167.1, 161.9, 161.5, 159.0, 156.2, 156.1, 147.6, 140.7, 136.5, 133.4, 133.3, 132.8, 129.4, 122.6, 120.4, 120.1, 119.9, 119.6, 116.9, 114.0, 113.8, 112.4, 112.2, 108.9, 108.6, 51.9, 45.2, 36.5, 32.6, 32.5, 26.6, 26.5, 25.5. HR-MS (APPI$^+$) calcd for $C_{29}H_{27}FN_2O_5H$ [M + H]$^+$: 503.1977; found: 503.1981.



Intermediate 58a

To a solution of compound **57** (500 mg, 0.995 mmol) in DMSO (5.0 mL) was added 4-(diethylamino)piperidine **a** (187 mg, 1.19 mmol) and TEA (432 μL, 3.10 mmol). Solid TBTU (415 mg, 1.29 mmol) was added in one portion and the mixture stirred at room temperature overnight. The mixture was diluted with *tert*-butyl methyl ether (*t*-BME; 50 mL) and 1 mol/L NaOH (45 mL) was added. The phases were separated. The aqueous layer was further extracted with *t*-BME (25 mL). The organic portions were combined, washed with water and brine, dried over Na_2SO_4, filtered, and evaporated to give a white foam (600 mg). This material was subsequently dissolved in DMSO (5 mL) and 10 mol/L NaOH (1.0 mL, 10 mmol) was added dropwise. The mixture was warmed to 50 °C and stirred for 30–60 min, then cooled to room temperature. Water (15 mL) was added, followed by the dropwise addition of 1.0 mol/L HCl until pH 4–5. During this process, a very fine white suspension was formed. The suspension was transferred to a centrifuge tube of appropriate volume and spun in a benchtop centrifuge at 3200 rpm for 5 min. The supernatant was removed and discarded. Water (15 mL) was added to the sediment, which was resuspended, and the mixture spun again. The supernatant was discarded and the procedure repeated once more. The wet solids were collected, dissolved in EtOH (30 mL), evaporated under reduced pressure, then dried at 50 °C under a high vacuum to afford compound **58a** (500 mg, 81% overall yield) that was used directly for inhibitor synthesis.

Intermediate 58b

In a manner similar to that for intermediate **58a**, compound **57** (500 mg, 0.995 mmol) and *n*-isopropyl piperazine **b** (153 mg, 1.19 mmol) provided compound **58b** (490 mg, 82% overall yield) that was used directly for inhibitor synthesis.

Inhibitor 34

To a solution of compound **58a** (53 mg, 0.085 mmol) in THF (2.5 mL) was added carbonyldiimidazole (55 mg, 0.34 mmol) and this was heated at 50 °C for 1 h. After cooling to room temperature, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 62 mg, 0.41 mmol) in THF (0.5 mL) and cyclopropylsulfonamide (5.8 mg, 0.048 mmol) in THF (0.5 mL) were added. This mixture was heated to 125 °C for 60 min in a sealed tube. The volatiles were then evaporated under reduced pressure and the residue dissolved in DMSO (2 mL). The desired material was isolated and purified using RP-prep HPLC using an ACN/water gradient incorporating 0.1% TFA as buffer. Following collection, pooling, and lyophilization of relevant fractions, compound **34** was obtained (43 mg) as a white amorphous bis-TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.92–11.86 (m, 1H), 9.12–9.00 (br s, 1H), 8.27 (dd, 1H, J = 1.5, 4.8 Hz), 8.07 (d, 1H, J = 14.7 Hz), 7.96 (ddd, 1H, J = 2.0, 7.3, 8.4 Hz), 7.89 (d, 1H, J = 8.6 Hz), 7.66 (dd, 1H, J = 1.4, 8.5 Hz), 7.45–7.23 (m, 3H), 7.23–7.10 (m, 2H), 5.26–5.09 (m, 1H), 4.86–4.64 (m, 1H), 4.38 (m, 1H), 4.0–3.7 (m, 2H), 3.61 (br s, 1H), 3.25–2.85 (m, 6H), 2.64 (m, 1H), 2.08–1.61 (m, 9H), 1.42–1.06 (m, 15H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.7, 165.5, 165.3, 162.1, 158.3, 157.9, 147.6, 140.7, 136.9, 133.4, 133.0, 129.4, 124.1, 120.4, 120.1, 120.0, 119.8, 118.7, 115.0, 112.3, 112.1, 111.7, 58.2, 44.4, 44.3, 42.7, 36.5, 32.6, 32.4, 31.0, 26.6, 25.7, 25.5, 9.9, 9.8, 9.7, 5.60. HR-MS (APPI$^+$) calcd for $C_{40}H_{48}FN_5O_5SH$ [M + H]$^+$: 730.3433; found: 730.3425.

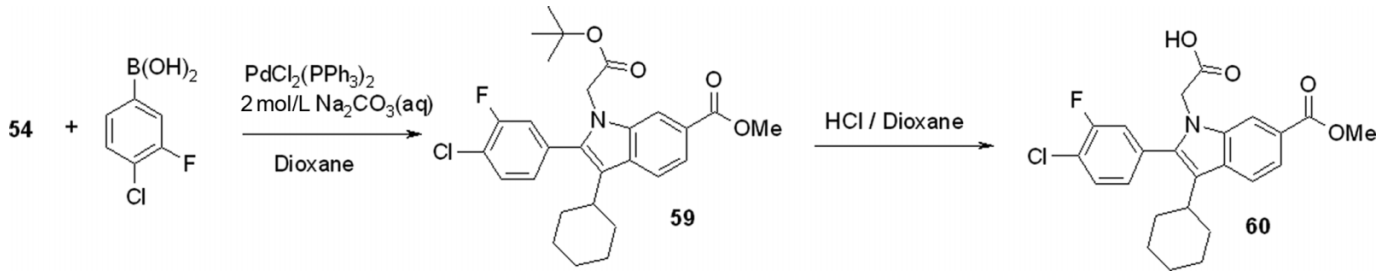
Inhibitor 41

In a similar manner to that for intermediate **34**, **41** was made using compound **58b** (53 mg, 0.085 mmol) and *N*,*N*-dimethylsulfamide (5.9 mg, 0.048 mmol), heating the mixture to 125 °C for 120 min in a sealed tube. Inhibitor **41** (50 mg) was obtained as a white amorphous bis-TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.62 (s, 1H), 9.75 (br s, 1H), 8.32–8.24 (m, 1H), 8.06 (s, 1H), 7.96 (ddd, 1H, J = 2.1, 7.2, 8.3 Hz), 7.87 (d, 1H, J = 8.4 Hz), 7.67 (dd, 1H, J = 1.4, 8.5 Hz), 7.41–7.28 (m, 2H), 7.26 (ddd, 1H, J = 0.9, 4.9, 7.2 Hz), 7.17 (d, 2H, J = 8.1 Hz), 5.33–5.07 (m, 1H), 4.95–4.72 (m, 1H), 4.46–4.33 (m, 1H), 4.19 (d, 1H, J = 13.6 Hz), 3.59–3.24 (m, 4H), 3.05–2.76 (m, 8H), 1.91–1.54 (m, 7H), 1.43–1.09 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.4, 162.0, 161.4, 159.0, 158.7, 158.4, 158.0,

156.1, 156.0, 147.6, 140.7, 136.9, 133.4, 129.2, 124.3, 120.3, 120.1, 119.7, 118.7, 117.9, 116.7, 114.9, 111.6, 57.4, 47.5, 38.0, 36.6, 32.6, 32.4, 26.7, 26.6, 25.5, 16.2. HR-MS (APPI$^+$) calcd for $C_{37}H_{45}FN_6O_5SH$ [M + H]$^+$: 705.3229; found: 705.3246.

In a similar fashion, inhibitors **35**, **40**, **46**, and **47** were made from the appropriated starting materials.

General procedure for the preparation of 30, 31, 36, 37, 42, and 43



Intermediate 59

Bromoindole **54** (8.00 g, 17.8 mmol) and 4-chloro-3-fluoro-phenylboronic acid (4.65 g, 26.6 mmol) were dissolved in dioxane (200 mL) and 2 mol/L Na_2CO_3 (32 mL, 64 mmol) was added. Argon gas was bubbled through the stirred mixture for 1 h. $PdCl_2(PPh_3)_2$ (630 mg, 0.89 mmol) was added and bubbling continued for a further 10 min. The mixture was heated to 100 °C and stirred for 12 h under an argon atmosphere. The reaction mixture was then cooled to room temperature and volatiles evaporated under reduced pressure. Ethyl acetate (200 mL) was added and the layers separated. The organic portion was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The compound was partially purified on silica gel, eluting with 10:1 hexane/EtOAc. The collected material was triturated with EtOAc/hexane mixtures, filtered, and dried under high vacuum to afford compound **59** has an off-white solid (6.65 g) that was used directly in the next step.

Intermediate 60

Ester **59** (6.65 g, 13.3 mmol) from the previous step was deprotected to give compound **60** in a manner similar to that described for compound **57**. Compound **60** was obtained as a white solid (5.34 g, 67% overall yield from bromoindole **54**). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.06 (br s, 1H), 8.09 (d, 1H, J = 1.2 Hz), 7.91 (d, 1H, J = 8.2 Hz), 7.80 (t, 1H, J = 8.2 Hz), 7.71 (dd, 1H, J = 1.6, 8.6 Hz), 7.42 (dd, 1H, J = 2.0, 9.8 Hz), 7.23 (dd, 1H, J = 1.6, 8.2 Hz), 4.83 (s, 2H), 3.89 (s, 3H), 2.62–2.54 (m, 1H), 1.96–1.62 (m, 7H), 1.40–1.13 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.3, 167.0, 158.1, 155.7, 137.4, 136.3, 131.9, 131.8, 131.0, 129.4, 127.9, 127.8, 122.7, 120.5, 120.3, 120.1, 119.8, 119.5, 118.8, 118.6, 112.0, 51.9, 45.3, 36.1, 32.7, 26.5, 25.5. HR-MS (APPI$^+$) calcd for $C_{24}H_{23}ClFNO_4H$ [M + H]$^+$: 444.1372; found: 444.1374.

Inhibitors 42 and 43

In a manner similar to that for compounds **58a** and **58b**, carboxylic acid **60** was coupled to racemic 2-(diethylamino) methyl morpholine and the methyl ester saponified to provide the desired indole carboxylic acid intermediate as a white solid in an 80% yield. Coupling, under conditions described for **34**, with cyclopropylsulfonamide and *N*,*N*-dimethylsulfamide provided inhibitors **42** and **43**.

Inhibitor 42

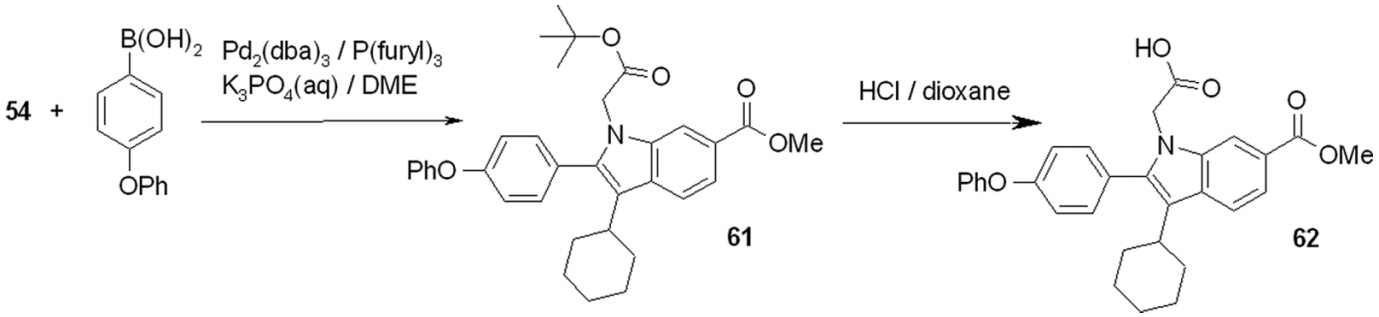
^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02–11.76 (m, 1H), 9.21 (br s, 1H), 8.04 (s, 1H), 7.89 (d, 1H, J = 8.6 Hz), 7.78 (s, 1H), 7.67 (d, 1H, J = 8.6 Hz), 7.39 (d, 1H, J = 9.5 Hz), 7.21 (d, 1H, J = 7.0 Hz), 5.15–4.90 (m, 2H), 4.31–4.10 (m, 1H), 4.00–3.80 (m, 2H), 3.72–3.25 (m, 3H), 3.23–3.06 (m, 7H), 3.02–2.77 (m, 1H), 2.63–2.52 (m, 1H), 1.97–1.60 (m, 7H), 1.45–0.97 (m, 13H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.7, 166.4, 166.3, 158.2, 158.1, 157.9, 155.6, 136.6, 130.9, 129.4, 127.9, 124.4, 120.0, 120.2, 120.0, 119.4, 118.9, 118.0, 111.7, 70.2, 65.8, 52.4, 48.0, 46.5, 45.0, 36.1, 32.7, 31.0, 26.5, 25.5, 8.7, 8.5, 8.2, 8.1, 5.6. HR-MS (APPI$^+$) calcd for $C_{35}H_{44}ClFN_4O_5SH$ [M + H]$^+$: 687.2778; 687.2788.

Inhibitor 43

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.73–11.50 (m, 1H), 9.36–9.16 (m, 1H), 8.05 (br s, 1H), 7.88 (d, 1H, J = 8.6 Hz), 7.84–7.74 (m, 1H), 7.68 (d, 1H, J = 8.4 Hz), 7.38 (d, 1H, J = 9.2 Hz), 7.20 (d, 1H, J = 7.3 Hz), 5.20–4.86 (m, 2H), 4.31–4.08 (m, 1H), 4.04–3.81 (m, 2H), 3.75–3.25 (m, 3H), 3.23–3.03 (m, 6H), 3.02–2.74 (m, 7H), 2.63–2.53 (m, 1H), 1.94–1.60 (m, 7H), 1.43–1.06 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.5, 166.4, 166.3, 158.2, 158.1, 157.8, 155.6, 137.7, 136.7, 132.2, 132.1, 129.2, 127.9, 124.5, 124.4, 120.2, 120.0, 119.3, 118.9, 111.5, 70.2, 65.8, 52.4, 51.7, 48.3, 48.0, 46.5, 45.0, 38.0, 36.1, 32.7, 26.5, 25.5, 8.7, 8.5, 8.2, 8.1. HR-MS (APPI$^+$) calcd for $C_{34}H_{45}ClFN_5O_5SH$ [M + H]$^+$: 690.2887; found: 690.2901.

Inhibitors **30**, **31**, **36**, and **37** were prepared in a similar fashion.

General procedure for the preparation of 29, 32, 33, 38, 39, 44, and 45



Intermediate 61

In a similar manner to that described for intermediate **59**, bromoindole **54** (10.0 g, 22.2 mmol) and 4-phenoxyphenylboronic acid (5.20 g, 24.4 mmol) were dissolved in DME (220 mL) and the mixture degassed for 30 min with bubbling argon gas. $Pd_2(dba)_3$ (330 mg, 0.355 mmol) and P(2-furyl)$_3$ (620 mg, 2.66 mmol) were added and degassing continued for another 15 min. Solid potassium phosphate (18.8 g, 88.8 mmol) was dissolved in predegassed water (110 mL) and this solution was added. The reaction was heated to 85 °C and stirred at this temperature for 16–20 h. After cooling to room temperature and dilution with EtOAc, the organic layers were separated, washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The product was purified on silica using 80:20 hexane/EtOAc as eluent. Compound **61** was obtained as a yellow oil (10.8 g) that was used directly in the next step.

Intermediate 62

Compound **61** (10.8 g) from the previous step was converted to compound **62** in a manner similar to that for compound **60**. Compound **62** was obtained as a white solid (5.30 g, 49% overall yield from bromoindole **54**). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.03 (br s, 1H), 8.04 (s, 1H), 7.88 (d, 1H, J = 8.2 Hz), 7.70 (dd, 1H, J = 1.4, 8.4 Hz), 7.52–7.44 (m, 2H), 7.39–7.33 (m, 2H), 7.27–7.21 (m, 1H), 7.20–7.12 (m, 4H), 4.79 (s, 2H), 3.88 (s, 3H), 2.60 (m, 1H), 1.93–1.65 (m, 7H), 1.39–1.15 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.2, 167.1, 157.4, 155.8, 139.5, 136.1, 132.0, 130.2, 129.7, 125.4, 124.2, 122.2, 119.8, 119.6, 119.4, 118.9, 118.0, 111.9, 51.8, 45.3, 36.1, 32.8, 26.6, 25.5. HR-MS (APPI$^+$) calcd for $C_{30}H_{29}NO_5H$ [M + H]$^+$: 484.2119; found: 484.2120.

Inhibitors 32 and 39

In the same manner as **42** and **43**, compound **62** was elaborated using appropriate reagents to provide the desired inhibitors **32** and **39** were made using cyclopropylsulfonamide and *N*,*N*-dimethylsulfamide, respectively, and isolated as their TFA salts.

Inhibitor 32

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (s, 1H), 9.10 (br s, 1H), 8.01 (d, 1H, J = 1.3 Hz), 7.87 (d, 1H, J = 8.6 Hz), 7.66 (dd, 1H, J = 1.4, 8.5 Hz), 7.50–7.43 (m, 2H), 7.35 (m, 2H), 7.26–7.16 (m, 3H), 7.15–7.08 (m, 2H), 4.94 (s, 2H), 4.43 (d, 1H, J = 12.5 Hz), 4.03 (d, 1H, J = 12.5 Hz), 3.71–3.55 (m, 1H), 3.28–3.05 (m, 4H), 3.04–2.89 (m, 1H), 2.74–2.57 (m, 2H), 2.07–1.64 (m, 8H), 1.55–1.03 (m, 14H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.7, 165.8, 158.3, 158.0, 157.6, 157.1, 156.1, 139.9, 136.4, 132.1, 130.2, 129.6, 126.0, 124.0, 123.7, 119.7, 119.0, 118.7, 118.6, 118.4, 111.5, 58.3, 45.0, 44.4, 44.3, 40.3, 36.1, 32.8, 31.0, 26.6, 26.4, 25.7, 25.5, 9.9, 9.8, 5.6. HR-MS (APPI$^+$) calcd for $C_{41}H_{50}N_4O_5SH$ [M + H]$^+$: 711.3575; 711.3585.

Inhibitor 39

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.60 (br s, 1H), 9.90 (br s, 1H), 8.02 (d, 1H, J = 1.2 Hz), 7.86 (d, 1H, J = 8.6 Hz), 7.68 (dd, 1H, J = 1.6, 8.6 Hz), 7.51–7.43 (m, 2H), 7.34 (m, 2H), 7.27–7.20 (m, 1H), 7.20–7.10 (m, 4H), 5.01 (d, 2H, J = 8.2 Hz), 4.45 (d, 1H, J = 11.7 Hz), 4.19 (d, 1H, J = 11.7 Hz), 3.65–3.31 (m, 4H), 3.08–2.84 (m, 8H), 2.75 (br s, 1H), 2.69–2.56 (m, 1H), 1.97–1.54 (m, 7H), 1.42–1.12 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.4, 166.3, 158.3, 158.0, 157.2, 156.0, 139.6, 136.5, 132.1, 130.2, 129.5, 125.8, 124.0, 123.9, 119.6, 119.1, 118.7, 118.6, 118.2, 111.5, 57.4, 47.5, 47.3, 44.8, 41.5, 38.0, 36.1, 32.8, 26.6, 25.5, 16.2. HR-MS (APPI$^+$) calcd for $C_{38}H_{47}N_5O_5SH$ [M + H]$^+$: 686.3371; found: 686.3388.

In a similar fashion, compounds **29**, **33**, **38**, **44**, and **45** were prepared from the appropriate starting materials.

X-ray crystallography

Protein crystallization

HCV strain 1b/J4 NS5B polymerase was purified as a protein construct that has the C-terminal 21 residues truncated and the C-terminal addition of a hexahistidine tag (NS5BΔ21). The protein was concentrated to 7.7 mg/mL and crystallized by the hanging drop vapor diffusion procedure using monomethyl ether polyethylene glycol as a precipitant (PEG5Kmme). In particular, 1 μL of NS5BΔ21 (in purification buffer (20 mmol/L tris pH 7.3, 300 mmol/L NaCl, and 10% glycerol)) was add to 1 μL of a solution made of 21% PEG5Kmme, 0.1 mol/L 2-(*N*-morpholino)ethanesulfonic acid (MES) pH 5.4, 10% glycerol, and 0.4 mol/L ammonium sulfate. The resulting 2 μL drop was suspended above a 1 mL reservoir solution made of 21% PEG5Kmme, 0.1 mol/L MES pH 5.4, 10% glycerol, and 0.4 mol/L ammonium sulfate.

Inhibitor soaking

Large single apo NS5BΔ21 crystals were soaked in a solution containing 1 mmol/L of the inhibitor for 5–6 h and then flash frozen in liquid nitrogen prior to diffraction data collection.

Data collection and processing

Diffractions were collected on a MicroMax-007 rotating anode X-ray generator equipped with a Raxis-IV++ image plate detector (Rigaku/MSC, USA). Data, to a resolution of 2.8 Å, was collected on a single crystal cryogenically cooled at –180 °C and processed with HKL-2000 software (HKL Research, USA).

Structure modeling and refinement

Phasing of the experimental data was done by molecular replacement using a published structure of apo NS5B (1C2J.pdb). Rotation and translation search as well as further structure refinement were done using the program CNX (Accelrys, USA). Model building was carried out with software O (Alwyn Jones, Upsala University, Sweden). The final model includes two molecules of NS5B (residues A1–A148, A153–A563, B1–B17, B36–B148, and B153–B563) and one ligand molecule associated with NS5B molecule B. The final crystallographic R factor is 21.9% and the R_{free} factor is 25.7% to a resolution of 2.7 Å. Data processing and model refinement statistics are included in the Supplementary data section. The coordinates and structure factors for the NS5B polymerase in complex with compound **12** have been deposited in the Protein Data Bank as entry 4GMC.

Biological testing

Inhibition of HCV NS5BΔ21 enzymatic activity was performed as previously described.[11a,20] The bicistronic luciferase reporter replicon, encoding the Con1 genotype *1b* NS2-NS5B coding region, and the experimental procedures for measuring EC_{50} values in the experiments reported within this article have been described elsewhere.[11a] Compounds were incubated with cells for 72 h and the relative levels of luciferase present were determined using the Bright-Glo luciferase substrate (Promega) on a Packard Topcount instrument. EC_{50} values were determined by the nonlinear regression routine NLIN procedure of SAS (EC_{50}). All reported values are the average of at least ≥2 measurements.

Pharmacokinetic experiments

All protocols involving animal experimentation were reviewed and approved by the local Animal Care and Use Committee. In-life procedures were in compliance with the Guide for the Care and Use of Laboratory Animals from the Canadian Council of Animal Care. All rat oral PK screen and distribution studies were performed at Boehringer Ingelheim (Canada) Ltd. using male Sprague–Dawley rats (275–300 g, Charles River, St-Constant, Quebec). Animals were fasted overnight with access to 10% dextrose in water, and each cassette containing four compounds (4 mg/compounds) was dosed (0.5% Methocel and 0.3% Tween-80) in two rats and plasma samples collected at 1 and 2 h postdosing. Plasma samples were extracted by solid-phase extraction using Waters Oasis HLB 60 mg cartridges. Samples were injected on an HPLC system (Waters Alliance 2690 or 600E System controller with 717+ autosampler and 625 pump) using a Waters XTerra C8 column (2.1 mm × 100 mm, 5 μmol/L). Detection was performed using an UV diode array (Waters PDA 996) between 200 and 400 nm with quantitative determination made by peak height at the wavelength representing the best signal-to-noise ratio. Calibration standards were prepared in blank plasma. The calibration curve was linear to cover the time–concentration curve with r^2 values >0.99 and a limit of detection (LD) ≤10 ng/mL. The temporal profiles of drug concentrations in plasma were analyzed by noncompartmental methods using WinNonlin (version 3.1; Scientific Consulting, Inc., Cary, North Carolina).

For liver exposure studies, liver samples were collected 2 h post the oral dose as follows: The rat liver was perfused with 25 mL ice-cold saline for 1 min prior to collection of the right lateral lobe. Both plasma and liver samples were extracted and analyzed by HPLC or LC/MS/MS as previously described.

Supplementary data

Suppmentary data (proton and mass spectral data for all inhibitors and data processing and model refinement statistics for the NS5B – inhibitor **12** complex) are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0319.

Acknowledgments

We thank the following colleagues from Boehringer Ingelheim (Canada) who participated in generating the data presented in this paper: N. Dansereau, L. Lagacée, M. Marquis, and C. Pellerin for IC_{50} and EC_{50} determinations; J. De Marte, F. Liard, H. Montpetit, and C. Zouki for ADME-PK profiling; N. Aubry for NMR support; and S. Bordeleau, C. Boucher, and S. Valois for analytical support.

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Further studies toward himandrine via sequential oxidative amidation – intramolecular Diels–Alder reactions

Takahito Kasahara and Marco A. Ciufolini

Abstract: Exploratory work toward the alkaloid himandrine evaluated the directing ability of a pyrrolidine C-3 substituent in a diastereotopic group elective intramolecular Diels–Alder reaction of a spirodienone obtained by the oxidative amidation of a phenol. The study also defined a technique for the construction of ring D of the alkaloid.

Key words: alkaloids, Diels–Alder, himandrine, hypervalent iodine, phenols.

Résumé : Des travaux préliminaires en vue de la synthèse de l'alcaloïde himandrine ont permis d'évaluer la possibilité d'un substituant en position C-3 d'une pyrrolidine d'orienter la réaction dans un groupe sélectif diastéréotope, d'une réaction de Diels-Alder intramoléculaire d'une spirodiénone obtenue par amidation oxydante d'un phénol. L'étude a aussi permis de définir une technique pour la formation du cycle D de l'alcaloïde.

Mots-clés : alcaloïdes, Diels-Alder, himandrine, iodure hypervalent, phénols.

[Traduit par la Rédaction]

Introduction

The architecturally interesting alkaloid himandrine (**1**)[1] invites the exploration of an approach that relies on a tandem oxidative amidation[2] – intramolecular Diels–Alder (IMDA)[3] reaction of phenolic sulfonamide **5**. According to the format of Scheme 1, unraveling of the "northeastern" quadrant of **1** produces simplified structure **2**, wherein substituent R and functionality Z would ultimately permit the formation of rings D–F of the natural product. Tricyclic compound **2** could be obtained from **3**, which is the result of an intramolecular Diels–Alder reaction occurring selectively at the pro-S double bond of dienone **4**. The latter is recognized as the product of oxidative cyclization[4] of **5**. Cycloadduct **3** exhibits the incorrect cis configuration of the decaline system relative to **2**, but the neighboring carbonyl group should enable epimerization to the more energetically favorable trans diastereomer.

The expectation that a dienone such as **4** should selectively undergo IMDA in the desired sense was rooted in the surmise that a Diels–Alder reaction occurring at the pro-R double bond (conformer *syn*-**4**, Scheme 2) would be impeded by steric compression between the sulfonyl group and substituents R and $(CH_2)_2Z$ at the C-5 and C-3 position of the pyrrolidine ring, respectively. Conversely, an IMDA reaction occurring at the pro-S double bond (*anti*-**4**) would be relatively free of nonbonding interactions. We describe product **6** as the syn cycloadduct (disfavoured) and compound **3** as the anti cycloadduct (favoured).

It should be noted that the N-bearing tetrasubstituted carbon atom in the dienone segment of compound **4** is chirotopic, but not stereogenic.[5] A generic addition reaction occurring selectively at either the pro-R or the pro-S double bond of the dienone, as exemplified in the conversion of *anti*-**4** to **3**, induces a well-defined configuration, R or S, at the level of the atom in question. The stereocontrolled generation of such tetrasubstituted carbon centers is generally difficult, but approaches based on a selective addition to one of the diastereotopic carbon–carbon π bonds in dienones of type **4** offers a good solution.[6] Of course, the honoree of the present issue of the *Canadian Journal of Chemistry* has contributed significantly to the development of this principle.[7]

A model study designed to address the feasibility of the foregoing tandem sequence employed simplified substrate **7** (Scheme 3),[8] wherein the N-bearing carbon is of opposite configuration relative to the corresponding centre in **4**. The CH_2OH group in **7** correlates with the R substituent in **4**. Relative to the latter, however, the $(CH_2)_2Z$ unit is absent. Oxidative cyclization[2] of **7** with the hypervalent iodine reagent,[9] (diacetoxyiodo)benzene ($PhI(OAc)_2$; DIB), in trifluoroacetic acid (TFA), followed by dilution with toluene and heating at reflux for 12 h, directly afforded the trans-fused compound **10**[10] as the major component of an 8:1 mixture of two cycloadducts.[11] Evidently, epimerization of the primary cycloadduct **9** had occurred in situ, probablybecause of reversible enol formation promoted by TFA. A mere hydroxymethyl

Received 10 September 2012. Accepted 16 November 2012. Published at www.nrcresearchpress.com/cjc on 15 January 2013.

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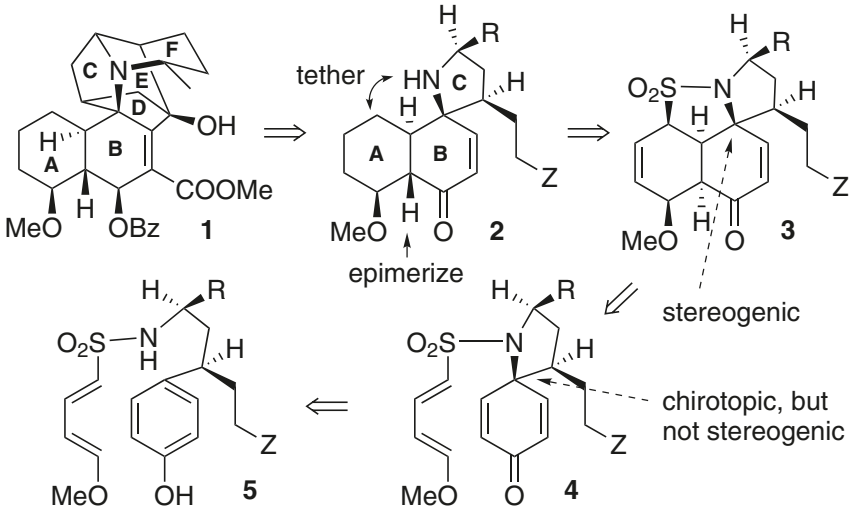
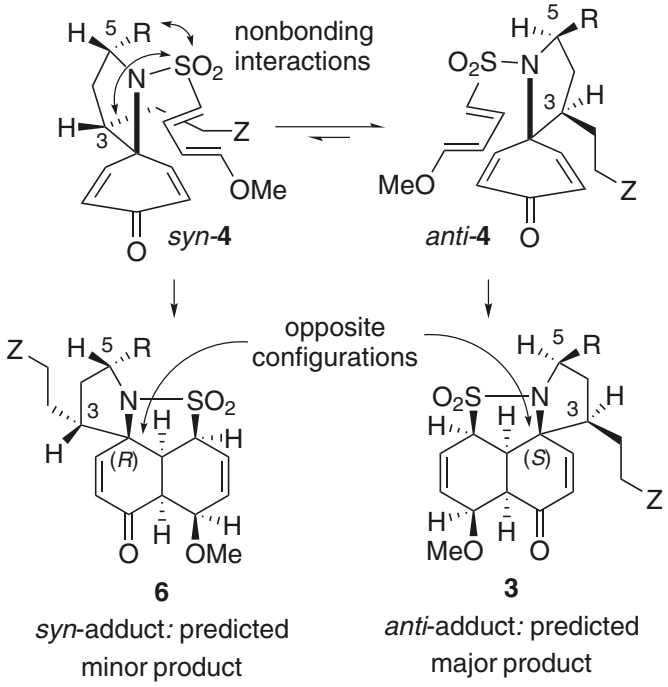
This article is part of a Special Issue dedicated to Professor Derrick Clive. It is a pleasure to dedicate this work to our friend and colleague, Professor Derrick L.J. Clive, in recognition of his many significant contributions to the field of organic chemistry.

Scheme 1.



Scheme 2.



group at the C-5 position of the pyrrolidine moiety of **8** had thus induced a satisfactory degree of diastereoinduction in the cycloaddition step. Our continuing pursuit of himandrine required knowledge of the directing effect of a C-3 group, which would correlate with the $(CH_2)_2Z$ substitution in **4**. Such studies could also define an appropriate functionality Z that might enable the formation of ring D of **1**. Results of investigations in this sense are described herein.

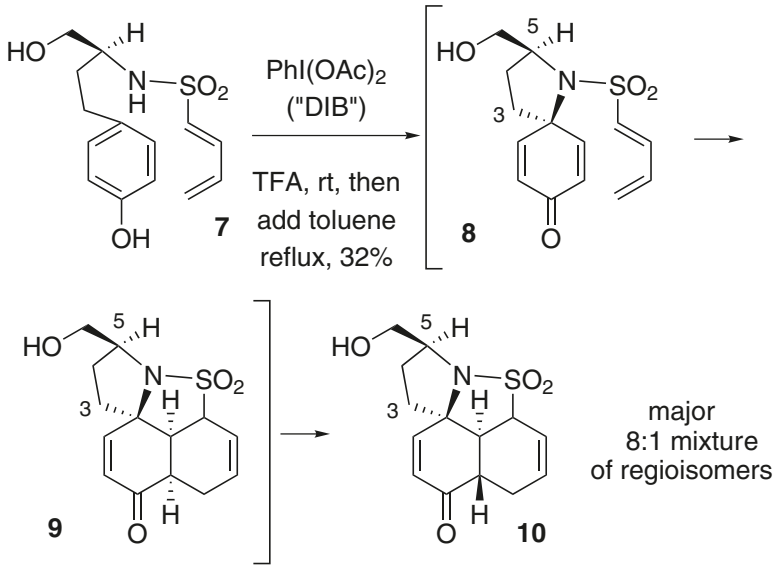
Results and discussion

The present work centred on substrate (±)-**11**, which by analogy with **4** and **7** would be processed through sequential oxidative cyclization and IMDA reactions (Scheme 4). The latter step could produce two pairs of diastereomeric adducts, arising through reaction in an anti (desired) or a syn (undesired) mode with either endo (presumably favoured on electronic grounds) or exo topology. These four compounds are shown in Scheme 4 as structures **13**–**16**. Base-promoted isomerization of **13** and **14** would then provide compound **17**, which possesses the correct relative configuration of all stereocentres as required for himandrine.

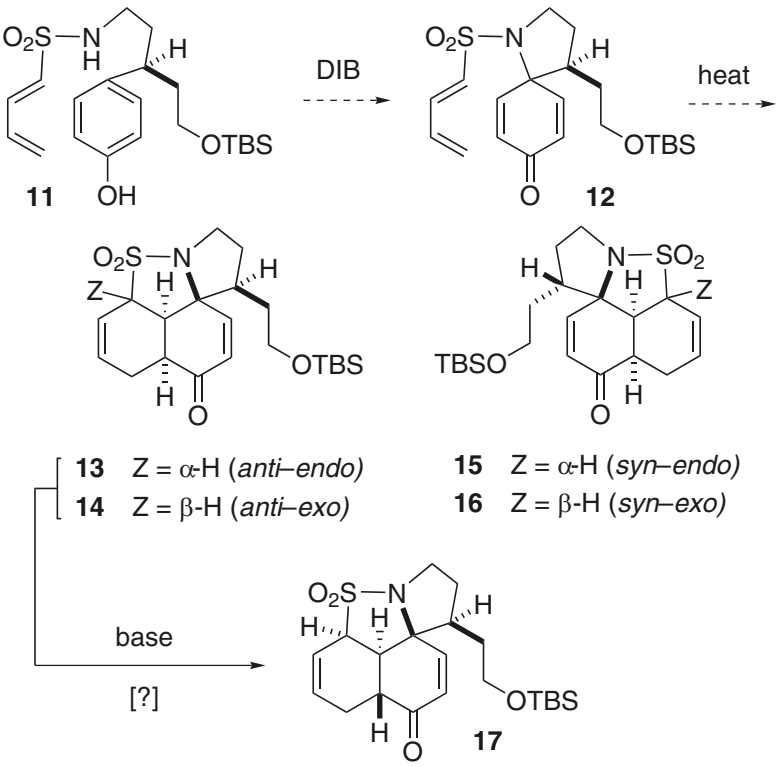
A computational study (MM+)[12] carried out with simplified structures **18**–**21**, which lack the *tert*-butyldimethylsiloxy (OTBS) group relative to **13**–**16**, revealed that the pair of endo adducts **18** (an analog of the desired **13**) and **20** (a surrogate of the undesired **15**) are virtually isoenergetic, whereas the anti-exo adduct **19** (cf. the serviceable **14**) was only slightly favoured relative to its diastereomer, **21** (Fig. 1; tabulated energies are relative to the least energetic compound, **18**). This result elicited some apprehension, in that, if the energies of the transition states leading to the various cycloadducts were also to be similar, then the crucial IMDA step would proceed with modest diastereoselectivity. On the other hand, calculations provided support for the prediction that structure **23**, which possesses a himandrine-like relative configuration, should be favoured over its diastereomers **18**–**22** (Fig. 2; tabulated energies are relative to the least energetic isomer, **23**). This boded well for the planned route to compound **17**.

The experimental verification of these hypotheses commenced with a Tozer-type[13] condensation of **24** (the preparation of this material is provided as Supplementary data) with acrolein, followed by selective desilylation of the phenol,[14] leading to dienic sulfonamide **11** (Scheme 5). Oxidative cyclization with DIB in CH_2Cl_2, in the presence of 1.1 equiv of TFA, afforded dienone **12**. Whereas similar dienones had previously been advanced directly to the Diels–Alder step,[8] the present work revealed that greater overall efficiency was attainable by purifying **12** prior to IMDA reaction. When a toluene solution of pure **12** was refluxed for 5 h, an IMDA reaction occurred, which led to a mixture of four compounds. These were ultimately assigned as the anti-endo (**13**), anti-exo (**14**), and syn-endo (**15**) adducts, plus some **17** (i.e., *epi*-**13**).

Scheme 3.



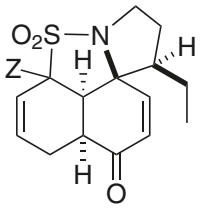
Scheme 4.

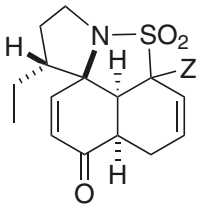


No evidence could be garnered for the presence of syn-exo cycloadduct **16**. A typical IMDA step would return an approximately 1.2:1.0:1.1 mixture of **13**, **14**, and **15**, respectively, containing a small amount of **17**. The extent of formation of the latter varied from batch to batch of material, and ranged from barely detectable to about 20%–25% of the product mixture. The presence of increased quantities of **17** was always accompanied by a corresponding decrease in **13**. We surmise that trace amounts of residual TFA were responsible for the in situ epimerization of **13** via acid-promoted enol formation. Notice that only **13** can isomerize to **17** under acidic conditions.

As anticipated, the action of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) upon the mixture of IMDA adducts resulted in the conversion of **13** and **14** into the desired **17**, while **15** advanced to **25**. Unsurprisingly, the isomerization of endo-adduct **13** was considerably faster than that of **14**, which also must undergo epimerization at the less

Fig. 1. Estimated energies (MM+, kcal/mol) of model endo and exo adducts **18**–**21** (1 cal = 4.194 J).

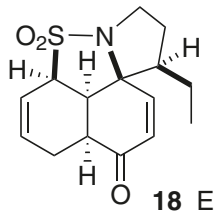




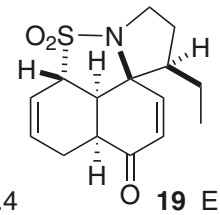
18 Z = α-H (*anti–endo*) E_{conf} = 0.0 **20** Z = α-H (*syn–endo*) E_{conf} = 0.2

19 Z = β-H (*anti–exo*) E_{conf} = 0.4 **21** Z = β-H (*syn–exo*) E_{conf} = 1.4

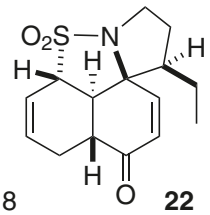
Fig. 2. Estimated energies (MM+, kcal/mol) of *trans*-decalin diastereomers of **18**–**19** (1 cal = 4.194 J).



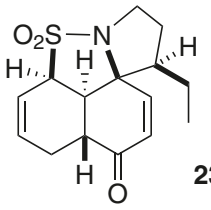
18 E = 4.4



19 E = 4.8



22 E > 10



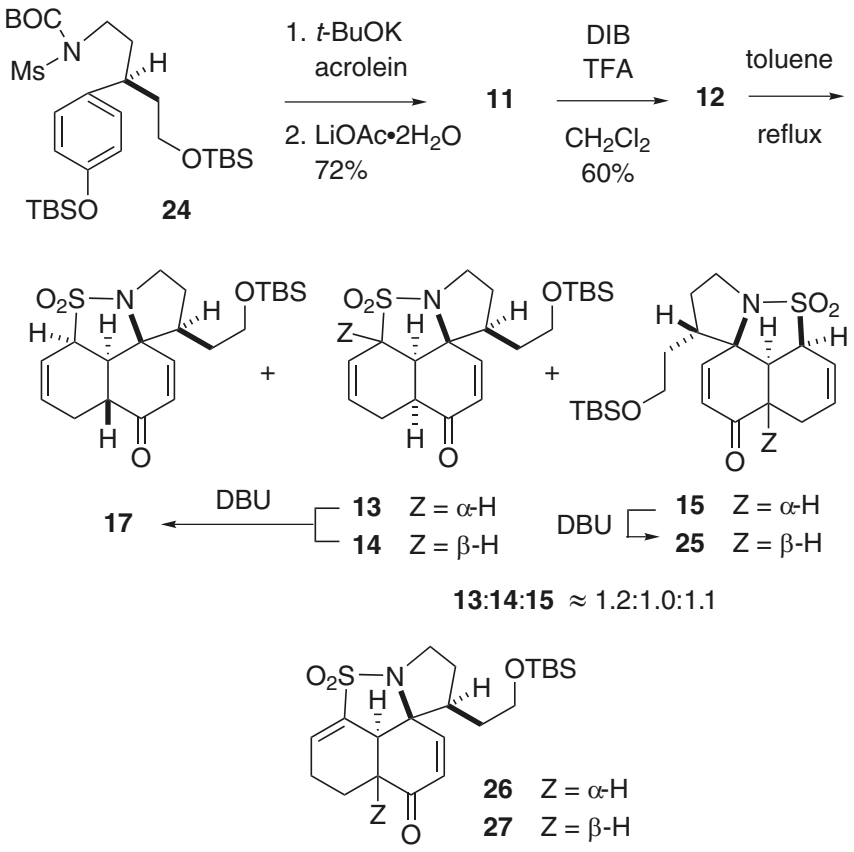
23 E = 0.0

acidic α position of the sulfonamide. The epimerization step was best carried out in toluene at 60 °C over 2 h, at which time approximately 30% of the starting **13** and **14** remained. Longer reaction times and (or) higher temperatures promoted the formation of two byproducts, assigned as vinylsulfonamides **26** and **27**.[15] Fortunately, the balance of **13** and **14** epimerized to **17** during a subsequent O-deprotection step.

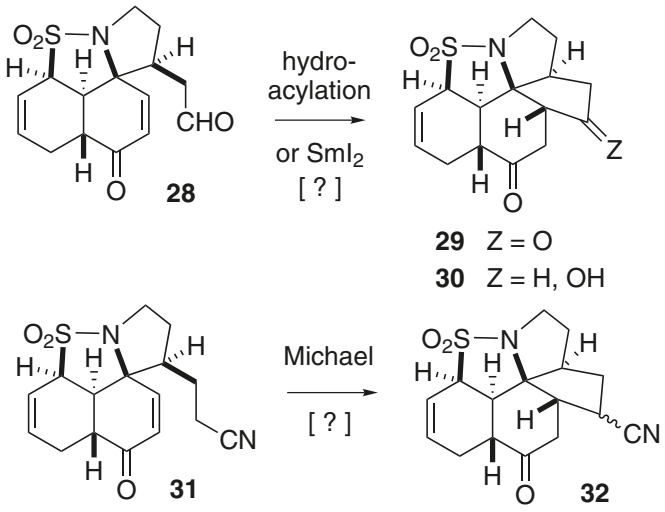
This preliminary phase of our study had determined that a linear alkyl group at the C-3 position of the pyrrolidine is weakly directing compared with a C-5 substituent, favouring the production of anti adducts to the extent of ~2:1. Still, the successful production of compound **17** enabled additional investigations that defined a method for the formation of ring D. To that end, we targeted aldehyde **28** and nitrile **31** (Scheme 6). The aldehyde appeared to be a substrate for cyclization in a hydroacylation (cf. **29**) or a reductive (cf. **30**) mode, whereas the nitrile might advance to **32** through an intramolecular Michael reaction. The aldehyde was secured starting with a tetrabutylammonium fluoride (TBAF) deprotection of **17** (Scheme 7). As alluded to earlier, such a treatment promoted the epimerization of residual **13** and **14** (or desilylated forms thereof). The resultant **33** was contaminated with approximately 15% of epimerized syn adduct **25**.[16] The separation of the two compounds was problematic given their essentially identical mobility on chromatographic supports. Accordingly, the mixture was used as follows in subsequent operations: removal of the undesired regioisomeric material was best achieved at the stage of a more advanced pentacyclic intermediate (vide infra). Dess–Martin oxidation of **33** furnished the requisite **28** in a 72% yield. However, as of this writing we have been unable to achieve cyclization of **28** to either **29** or **30**.

Nitrile **31** was obtained from **33** as outlined in Scheme 8. Again, the final product was contaminated with approximately 15% of an isomer originating from **25**. Attempted base-promoted cyclization of **31** (*t*-BuOK) provided a mixture of uncharacterized products. Suspecting that the problem was due to preferential enolization of the ketone, an event that might trigger numerous undesired side reactions, the cyano group was converted into a more readily enolized aldehyde. The action of diisobutylaluminum hydride (DIBAL) upon **31** induced reduction of the ketone to an alcohol and of the nitrile to an aldehyde, necessitating a subsequent Dess–Martin oxidation to create the desired **35** (also containing ~15% of an isomer derived from **25**). The intramolecular Michael reaction of the latter under basic conditions was still problematic; however, treatment with pyrrolidine triggered cyclization to **36**, presumably through an enamine intermediate (Scheme 9). Separation of isomeric materials emanating from syn adduct **25** was achieved at this stage. However, the final compound was obtained as an essentially 1:1 mixture of epimeric aldehydes. This detracted nothing from the valuable information acquired, i.e., that ring D formation was achievable through the enamine-mediated intramolecular conjugate addition of **35**.

Scheme 5.



Scheme 6.



In summary, exploratory work toward himandrine determined that a C-3 substituent on the pyrrolidine moiety of **12** is weakly anti directing, and that the construction of ring D may be achieved through cyclization of a transient enamine formed in situ from aldehyde **35**. These results are essential to the progress of our ongoing effort toward the natural product. Further results in that sense will be disclosed in due course.

Experimental section

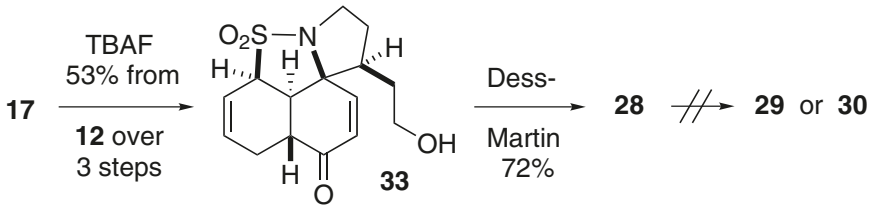
Experimental protocols (additional details are provided as Supplementary data)

Unless otherwise stated, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at room temperature (rt) from $CDCl_3$ solutions. Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, *J*, are in hertz (Hz). Multiplicities are reported as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), q (quartet), and m (multiplet), and further qualified as app (apparent) and br (broad). Flash chromatography was performed on 230–400 mesh silica gel.

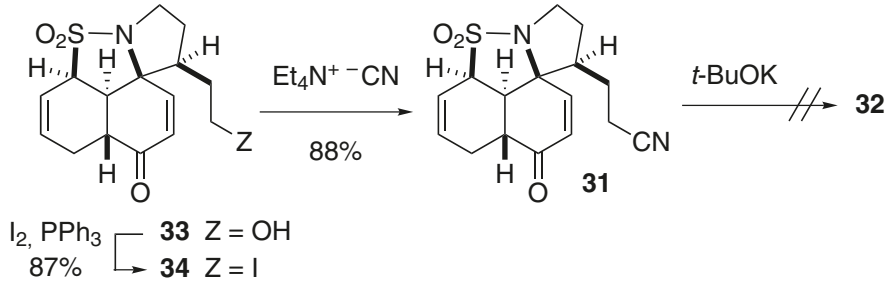
*(1E)-N-1-[[[5-(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[4-(1,1-dimethylethyl)dimethylsilyl]-oxy]-phenyl]pentyl]-1, 3-butadiene-1-sulfonamide (***11***)*

A freshly prepared tetrahydrofuran (THF) solution of KO-*t*-Bu (23 mL, 46 mmol, 2.0 mol/L, 3.5 equiv) was added dropwise to a solution of *N*-Boc sulfonamide **24**[16] (7.94 g, 13.2 mmol, 1.00 equiv) in THF (16 mL) at –78 °C. The resulting pale yellow solution was stirred for 1 h at –78 °C and a solution of acrolein (1.2 mL, 16.1 mmol, 1.2 equiv) in THF (11 mL) was added dropwise. The light green mixture was stirred for 1 h at –78 °C, then gradually warmed up to rt and stirred overnight (12 h). The resulting brown solution was quenched with sat. aq NH_4Cl (10 mL) and diluted with EtOAc (20 mL). The biphasic mixture was filtered through a pad of

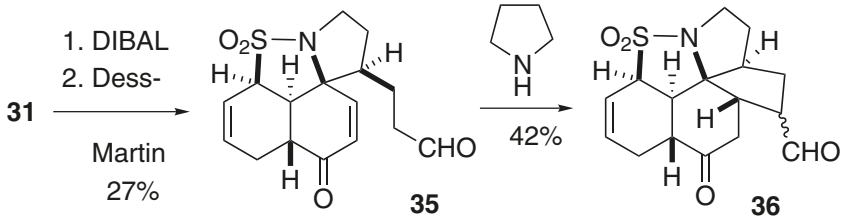
Scheme 7.



Scheme 8.



Scheme 9.



Celite with EtOAc (60 mL). The mixture was separated and the organic layer was rinsed again with sat. aq NH_4Cl. The combined aqueous phases were extracted twice with EtOAc (10 mL). The organic fractions were combined, rinsed with brine (10 mL), dried (Na_2SO_4), and concentrated to give a brown oil that contained white solids. The crude product was filtered through a pad of Celite with EtOAc (50 mL) and the filtrate was evaporated. To the residual brown oil (6.83 g, 12.7 mmol, 1.0 equiv) in dimethylformamide (DMF; 35 mL) was added $LiOAc{\cdot}2H_2O$ (259 mg, 0.2 equiv) and water (0.72 mL), and stirred at 75 °C for 6 h. The reaction was cooled to rt, diluted with EtOAc (70 mL), and washed twice with sat. aq NH_4Cl (20 mL). The combined aqueous layers were back-extracted three times with EtOAc (20 mL). The combined organic fractions were rinsed three times with brine (20 mL), dried (Na_2SO_4), and concentrated to furnish a brown oil. Purification by column chromatography (20% → 40% EtOAc/hexanes) afforded compound **11** (4.03 g, 72%) as a viscous pale yellow oil. IR: 3287, 2930, 2857, 1515. ^{1}H NMR δ: 7.01–6.90 (m, 3H), 6.77–6.70 (m, 2H), 6.34 (dt, J = 16.9, 10.4 Hz, 1H), 6.15 (d, J = 14.9 Hz, 1H), 6.02 (br s, 1H), 5.61 (d, J = 16.9 Hz, 1H), 5.53 (d, J = 10.2 Hz, 1H), 4.51 (br t, J = 6.0 Hz, 1H), 3.52–3.33 (m, 2H), 2.83 (br q, J = 6.7 Hz, 2H), 2.70 (app septet, J = 4.9 Hz, 1H), 1.94–1.63 (m, 4H), 0.86 (s, 9H), –0.02 (s, 6H). ^{13}C NMR δ: 154.6, 141.8, 135.3, 132.7, 128.8, 128.3, 127.4, 115.7, 61.1, 41.5, 39.9, 38.9, 37.0, 26.2, 18.5, –5.10, –5.14. HR-MS calcd for $C_{21}H_{36}NO_4SSi$ $[M + H]^+$: 426.2134; found: 426.2133.

***(±)-1-[1-((E)-1,3-Butadienyl)sulfonyl]-4-[1-[2-[(1,1-dimethylethyl)dimethylsilyl]-oxy]ethyl]-8-oxo-1-azaspiro[4.5]deca-6,9-diene* (12)**

The following procedure was performed with nonflame-dried glassware and unpurified solvents. A solution of sulfonamide **11** (3.01 g, 7.07 mmol, 1.0 equiv) in CH_2Cl_2 (35 mL) was added dropwise (addition funnel) over 8 min into a cooled (0 °C) solution of DIB (2.56 g, 7.79 mmol, 1.1 equiv) and TFA (600 μL, 7.79 mmol, 1.1 equiv) in CH_2Cl_2 (39 mL). The addition funnel originally containing the solution of **11** was rinsed twice with CH_2Cl_2 (2 mL), and the washes were added to the reaction mixture. The reaction was allowed to warm up and stirred for an additional 45 min at rt. Anhydrous K_2CO_3 (20 mg) was added, and the light brown suspension was concentrated to give an orange oil, which was purified by column chromatography (25% → 30% EtOAc/hexanes) to afford dienone **12** (1.57 g, 52%) as a viscous orange oil. IR: 2930, 2857, 1669, 1343. ^{1}H NMR δ: 7.00 (app dd, J = 14.9, 10.9 Hz, 1H), 6.82 (app dd, J = 9.9, 2.7 Hz, 1H), 6.67 (app dd, J = 10.6, 3.3 Hz, 1H), 6.39 (dt, J = 16.9, 10.3 Hz, 1H), 6.32–6.26 (m, 2H), 6.19 (d, J = 14.9 Hz, 1H), 5.66 (d, J = 16.9 Hz, 1H), 5.58 (d, J = 10.1 Hz, 1H), 3.65–3.52 (m, 4H), 2.52–2.30 (m, 2H), 1.84–1.67 (m, 1H), 1.41–1.29 (m, 1H),

1.23–1.10 (m, 1H), 0.85 (s, 9H), –0.01 (s, 6H). ^{13}C NMR δ: 185.4, 151.3, 145.8, 142.8, 132.5, 130.2, 129.1, 127.9, 126.8, 66.6, 61.0, 47.9, 47.7, 31.7, 29.8, 26.0, 18.3, –5.27, –5.33. HR-MS calcd for $C_{21}H_{33}NO_4SSiNa$ $[M + Na]^+$: 446.1797; found: 446.1801.

***(3aR*,8S*,8aS*,11aR*,11bR*)-1,3a,7,8,11a,11b-Hexahydro-8-[[2-(1,1-dimethylethyl)-dimethylsilyl]-oxy)ethyl]-6H,11H-naphtho[1,8-cd]pyrrolo[1,2-b]isothiazol-11-one-4,4-dioxide* (17)**

A degassed (Ar bubbling, sonication, 15 min) solution of dienone **12** (1.57 g, 3.71 mmol, 1.0 equiv) in toluene (9.0 mL) was heated to 120 °C (oil bath temperature) for 5 h, whereupon disappearance of the starting material was observed by ^{1}H NMR. The solution was cooled to rt and diluted with more toluene (9.6 mL). Neat DBU (165 μL, 1.10 mmol, 0.3 equiv) was added; the solution was again degassed with Ar (5 min) and then heated to 58 °C (oil bath temperature) for 2 h. The mixture was cooled to rt, diluted with EtOAc (20 mL), and washed with sat. aq NH_4Cl (10 mL). The organic phase was separated and washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give crude **17** (1.53 g, contaminated with isomers as per the discussion) as a brown oil. This crude material was used without further purification. A 70% pure sample was prepared as follows: Upon completion of the IMDA reaction, the solvent was evaporated and the residue was subjected to column chromatography (20% EtOAc/hexanes). Fractions containing the anti-endo adduct **13** and some anti-exo adduct **14**, plus compound **17** arising through in situ epimerization of **13**, were combined and evaporated to afford an ~26:10:64 mixture of the three isomers, respectively. This material was dissolved in enough toluene to furnish a 0.2 mol/L solution of substrates, to which DBU (0.4 equiv) was added. The mixture was stirred at 40 °C (oil bath temperature) for 3 h, then it was cooled to room temperature, diluted with EtOAc (5 mL), rinsed with sat. aq NH_4Cl solution, washed with brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography (20% EtOAc/hexanes) afforded compound **17**, clear film, contaminated with about 15% each (^{1}H NMR) of vinyl sulfonamides **26** and **27**. These produced characteristic signals at 6.83 ppm (app q, J = 3.3 Hz) and 6.75 ppm (app q, J = 3.3 Hz). IR: 2955, 2930, 2857, 1693, ^{1}H NMR δ: 6.48 (d, J = 10.4 Hz, 1H), 6.35–6.27 (m, 1H), 6.18 (d, J = 10.4 Hz, 1H), 5.89–5.81 (m, 1H), 3.92–3.78 (m, 2H), 3.71–3.40 (m, 4H), 2.69 (dd, J = 13.7, 7.1 Hz, 1H), 2.65–2.55 (m, 1H), 2.43–2.31 (m, 1H), 2.19–2.03 (m, 2H), 1.92–1.74 (m, 1H), 1.51–1.40 (m, 2H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR δ: 198.1, 142.6, 135.3, 130.0, 115.9, 68.9, 60.8, 57.8, 48.5, 45.4, 40.2, 38.7, 32.0, 30.3, 25.97, 18.3, 24.3, –5.3. 1151. HR-MS calcd for $C_{21}H_{33}NO_4SSiNa$ $[M + Na]^+$: 446.1797; found: 446.1794.

***(3aR*,8S*,8aS*,11aR*,11bR*)-1,3a,7,8,11a,11b-Hexahydro-8-[[2-hydroxyethyl]-6H,11H-naphtho[1,8-cd]pyrrolo[1,2-b]isothiazol-11-one-4,4-dioxide* (33)**

A cold (–25 °C) solution of the crude tetracycle **17** (1.53 g, produced from 1.57 g (3.71 mmol) of dienone **12** as detailed previously) in THF (7.2 mL) was treated with TBAF (commercial 1 mol/L solution in THF; 11.0 mL, 11.0 mmol, 1.0 mol/L, 3.0 equiv). The resulting dark brown mixture was stirred at –25 °C for 4 h, then water (10 mL) was added dropwise and the mixture was warmed to rt and diluted with EtOAc (20 mL). The organic phase was separated and the aqueous layer was extracted three times with EtOAc (3 mL). The organic phases were combined, rinsed with water (5 mL) and then with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography (90% EtOAc/hexanes → EtOAc) afforded alcohol **33** (615 mg, 1.99 mmol, 53% over three steps from **12**) as a white foam. This material contained approximately 15% of the isomer emanating from compound **25**. IR: 3529, 2936, 2894, 1689, 1306, ^{1}H NMR δ: 6.47 (d, J = 10.4 Hz, 1H), 6.35–6.27 (m, 1H), 6.17 (d, J = 10.4 Hz, 1H), 5.88–5.80 (m, 1H), 3.96–3.89 (m, 1H), 3.88–3.69 (m, 2H), 3.66–3.38 (m, 3H), 2.68 (dd, J = 13.6, 7.1 Hz, 1H), 2.65–2.54 (m, 1H), 2.46–2.34 (m, 1H), 2.20–2.04 (m, 2H), 1.91–1.74 (m, 1H), 1.68 (br s, 1H), 1.60–1.35 (m, 2H). ^{13}C NMR δ: 198.1, 142.6, 135.3, 130.0, 115.7, 68.9, 60.7, 57.8, 48.5, 45.6, 40.2, 38.7, 31.6, 30.0, 24.2. 1148. HR-MS calcd for $C_{15}H_{19}NO_4SNa$ $[M + Na]^+$: 332.0932; found: 332.0935.

***(3aR*,8S*,8aS*,11aR*,11bR*)-1,3a,7,8,11a,11b-Hexahydro-8-[[2-iodoethyl]-6H,11H-naphtho[1,8-cd]pyrrolo[1,2-b]isothiazol-11-one-4,4-dioxide* (34)**

Solid I_2 (506 mg, 1.99 mmol, 2.3 equiv) was added to a chilled (0 °C) solution of alcohol **33** (265 mg, 867 μmol, 1.0 equiv), PPh_3 (459 mg, 1.75 mmol, 2.0 equiv), and imidazole (148 mg, 2.17 mmol, 2.5 equiv) in THF (2.8 mL). After 5 min, the reaction flask was taken out of the ice bath and the solution was stirred at rt for 2 h. The mixture was diluted with EtOAc (10 mL) and rinsed twice with 10% aq $Na_2S_2O_3$ solution (5 mL). The combined aqueous phases were back-extracted once with ethyl acetate (3 mL). The combined organic phases were rinsed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (30% → 40% EtOAc/hexanes) afforded the title compound (318 mg, 87%) as a yellow solid; mp 189–192 °C (dec.). This material contained approximately 15% of the isomer emanating from compound **25**. IR: 2934, 2898, 1689, 1306, 1137. ^{1}H NMR δ: 6.45 (d, J = 10.4 Hz, 1H), 6.36–6.28 (m, 1H), 6.17 (d, J = 10.4 Hz, 1H), 5.89–5.82 (m, 1H), 3.98–3.81 (m, 2H), 3.58–3.38 (m, 2H), 3.35–3.26 (m, 1H), 3.09–2.98 (m, 1H), 2.66–2.55 (m, 2H), 2.45–2.34 (m, 1H), 2.20–2.02 (m, 2H), 1.84–1.61 (m, 3H). ^{13}C NMR δ: 197.7, 142.1, 135.3, 130.2, 115.6, 68.5, 57.7, 49.2, 48.1, 40.1, 38.6, 32.6, 29.0, 24.2, 4.0. HR-MS calcd for $C_{15}H_{19}INO_3S$ $[M + H]^+$: 420.0130; found: 420.0130.

***3-((3aR*,3a^{1}R*,8R*,8aS*,11aR*)-1,3a,3a^1,6,7,8,11,11a-Octahydronaphtho[1,8-cd]pyrrolo[1,2-b]isothiazol-8-yl)-11-oxo-propanenitrile-4,4-dioxide* (31)**

Solid Et_4N^+ $^-$CN (132 mg, 0.794 mmol, 1.1 equiv) was added in one portion to a chilled (0 °C) solution of iodide **34** (300 mg, 0.716 mmol, 1.0 equiv) in MeCN (2.4 mL). The reaction flask was taken out of the ice bath and stirred at rt for 30 min. The suspension was diluted with EtOAc (5 mL) and rinsed twice with 10% $Na_2S_2O_3$ aqueous solution (2 mL). The aqueous fractions were combined and extracted three times with EtOAc (1 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (60% → 65% EtOAc/hexanes) afforded **31** (200 mg, 88%) as a white solid; mp 183–187 °C (dec.). This material contained approximately 15% of the isomer emanating from compound **25**. IR: 2936, 2248, 1690, 1307, 1148. ^{1}H NMR δ: 6.45 (d, J =

10.5 Hz, 1H), 6.37–6.28 (m, 1H), 6.21 (d, J = 10.5 Hz, 1H), 5.89–5.81 (m, 1H), 3.98–3.83 (m, 2H), 3.61–3.51 (m, 1H), 3.50–3.39 (m, 1H), 2.68–2.31 (m, 5H), 2.20–1.98 (m, 2H), 1.93–1.80 (m, 1H), 1.76–1.62 (m, 1H), 1.61–1.46 (m, 1H). ^{13}C NMR δ: 197.6, 141.5, 135.4, 130.6, 118.5, 115.5, 68.6, 57.7, 48.3, 47.9, 40.2, 39.0, 29.3, 25.1, 24.2, 16.5. HR-MS calcd for $C_{16}H_{18}N_2O_3SNa$ [M + Na]$^+$: 341.0936; found: 341.0949.

***3-((3aR*,3a¹R*,8R*,8aS*,11aR*)-1,3a,3a¹,6,7,8,11,11a-Octahydronaphtho[1,8-cd]pyrrolo[1,2-b]isothiazol-8-yl)-11-oxo-propanal-4,4-dioxide* (35)**

Commercial DIBAL in hexanes (1 mol/L, 0.25 mL, 0.25 mmol, 3.0 equiv) was added dropwise to a cold (–78 °C) solution of **31** (26 mg, 0.082 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL). The mixture was stirred at –78 °C for 5 h, and then it was quenched by careful addition of MeOH (0.1 mL). The reaction was taken out of the cold bath, diluted with EtOAc (2 mL), and treated with sat. aq Rochelle's salt solution (2 mL). The resulting biphasic mixture was vigorously stirred overnight at rt. The organic phase was separated and the aqueous layer was extracted three times with EtOAc (1 mL). The combined organic phases were rinsed with brine, dried (Na_2SO_4), and concentrated. The crude product, a mixture of diastereomers of the secondary alcohol, was directly dissolved in CH_2Cl_2 (0.35 mL) and Dess–Martin periodinane (52 mg, 0.12 mmol, 1.5 equiv) was added in one portion. The white suspension was allowed to stir at rt for 2 h. The reaction was diluted with EtOAc (2 mL) and rinsed twice with 1:1 (v/v) 10% aq $Na_2S_2O_3$ / sat. aq $NaHCO_3$ (1 mL). The combined aqueous layers were back-extracted three times with EtOAc (1 mL). The combined extracts were rinsed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (75% → 80% EtOAc/hexanes) gave **35** as a clear film (7 mg, 27%). This material contained approximately 15% of the isomer emanating from compound **25**. IR: 2927, 1719, 1690, 1307, 1148. ^{1}H NMR δ: 9.76 (br s, 1H), 6.47 (d, J = 10.5 Hz, 1H), 6.36–6.28 (m, 1H), 6.20 (d, J = 10.5 Hz, 1H), 5.89–5.81 (m, 1H), 3.93–3.76 (m, 2H), 3.56–3.37 (m, 2H), 2.74 (dd, J = 13.6, 7.1 Hz, 1H), 2.68–2.48 (m, 3H), 2.35–2.25 (m 1H), 2.21–2.07 (m, 1H), 1.93–1.64 (m, 3H), 1.44–1.29 (m, 1H). ^{13}C NMR δ: 200.7, 197.8, 142.1, 135.3, 130.3, 115.6, 69.0, 57.8, 48.2, 48.0, 42.0, 40.2, 38.6, 29.7, 24.2, 21.1. HR-MS calcd for $C_{17}H_{24}NO_5S$ [M + MeOH + H]$^+$: 354.1375; found: 354.1387.

***Compound* 36**

Pyrrolidine (49 μL, 593 μmol, 10 equiv) was added to solution of aldehyde **35** (19 mg, 59 μmol, 1.0 equiv) in THF (0.6 mL) at rt. The mixture was heated to 30 °C (oil bath temperature) and stirred for 14 h, then it was quenched with 1 mol/L HCl (1 mL), stirred for 30 min at rt, and then diluted with EtOAc (3 mL). The organic phase was separated and the aqueous layer extracted five times with EtOAc (1 mL). The combined extracts were rinsed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (70% EtOAc/hexanes) afforded pentacyclic substance **36** (8 mg, 42%, clear film) as a 1:1 mixture of α- and β-aldehyde diastereomers. This material was free of isomeric products emanating from compound **25**. IR: 2936, 1716, 1151. ^{1}H NMR δ: 9.79 (s, 1H) and 9.70 (s, 1H), 6.31–6.22 (m, 2H), 5.88–5.78 (m, 2H), 4.15–4.04 (m, 1H), 3.86–3.76 (m, 1H), 3.58–3.08 (m, 9H), 2.75 (d, J = 5.4 Hz, 1H), 2.69 (d, J = 5.4 Hz, 1H), 2.60–2.28 (m, 7H), 2.27–2.17 (m, 3H), 2.14–2.00 (m, 3H), 1.98–1.78 (m, 4H), 1.66–1.55 (m, 2H). ^{13}C NMR δ: 209.6, 209.0, 200.7, 199.7, 134.5, 134.4, 115.7, 115.5, 79.7, 79.2, 60.54, 60.51, 56.0, 55.2, 52.1, 52.0, 51.7, 50.2, 44.52, 44.48, 43.5, 42.6, 41.7, 41.6, 41.3, 37.3, 32.9, 30.3, 28.7, 27.5, 24.4 (two signals). HR-MS calcd for $C_{16}H_{20}NO_4S$ [M + H]$^+$: 322.1113; found: 322.1109.

Supplementary data

Supplementary data (experimental procedures for the preparation of compound **24** and characterization data) are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0340.

Acknowledgments

We thank the University of British Columbia, the Canada Research Chair Program, the Canada Foundation for Innovation (CFI), the British Columbia Knowledge Development Fund (BCKDF), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Canadian Institutes of Health Research (CIHR) for financial support.

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